EXHIBIT 25

Periodic Safety Update Report

Oxycodone Hydrochloride Preparations

Report Period:

13 April 2009 through 12 October 2009

Date of Report:

10 December 2009

PERIODIC SAFETY UPDATE REPORT FOR: Oxycodone hydrochloride preparations

CONFIDENTIAL
Oxycodone Periodic Safety Update Report
Report Period: 13APR2009 – 12OCT2009

PERIODIC SAFETY UPDATE REPORT FOR: Oxycodone hydrochloride preparations

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PERIOD COVERED BY THIS REPORT:	13 April 2009 through 12 October 2009
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Periodic Safety Update Report (PSUR)

Executive Summary

This is the 19th PSUR for oxycodone. Oxycodone is a semi-synthetic opioid derived from the opium alkaloid, thebaine, and shares certain physicochemical characteristics and opioid receptor agonist activity with morphine and other similar opioids. The principal pharmacological actions are analgesia and effects on the central nervous system and smooth muscle. Oxycodone is controlled internationally under Schedule I of the Single Convention on Narcotic Drugs of 1961 and has been used as an analgesic for over 80 years.

Oxycodone-containing products are currently used clinically in many countries for treatment of moderate to severe pain. Oxycodone is available in immediate-release and controlled-release oral preparations and in parenteral formulations, and is manufactured and marketed globally by, among others, the Purdue/Mundipharma/Napp independent associated companies. This report includes suspected adverse drug reactions, and other data received or solicited by the Purdue/Mundipharma/Napp (PMN) independent associated companies, and is submitted on behalf of these companies. The oxycodone CCDS was revised during the reporting period for this PSUR, the most recent update for the CCDS was 07 August 2009.

Units equaling a total of about 7,813,224 patient months of exposure were distributed in the reference period. This is less than the 8,779,809 patient months reported in the previous reporting period and is largely due to a decrease in the market share of OxyContin® drug sales. In addition to the market patient exposure data, patients are being exposed in a number of ongoing clinical studies involving oxycodone.

Three (3) company-sponsored clinical studies and no non-clinical trials were completed and newly analyzed during the report interval of 13 April 2009 through 12 October 2009; two (2) were completed in China and one (1) in Slovakia. These three trials did not have an impact on the safety information provided within the CCDS. There were fourteen (14) clinical and no non-clinical trials planned, initiated, or continuing during the reporting interval of 13 April 2009 through 12 October 2009. Of note, studies are included if relevant safety data has been collected, whether or not the stated primary or secondary endpoint is safety related. None of the studies included in this report specifically investigated a primary safety related endpoint.

The Purdue/Mundipharma/Napp (PMN) Drug Safety and Pharmacovigilance Departments received or created 2,394 cases, initial and follow-up reports, from worldwide sources reporting events temporally associated with an oxycodone-containing product. This number is slightly increased as compared to the number of cases received / created during the last reporting interval (2,342). Given the decreased patient exposure, the overall reporting rate for the period has increased. The increase is due to the increased number of cases received through US litigation cases during the current period (714 cases) as compared to the previous reporting period (397 cases). The number of non-litigation cases received (1,680) was in fact lower than that received (1,945) during the last reporting interval.

The total number of cases (legal and non-legal) meeting ICH E2C criteria for inclusion into this PSUR was 432. This number is decreased as compared to the number of cases that met inclusion

criteria for the last reporting period (766). The decreased number of cases is largely due to a decreased number of legal cases (48 versus 266) that met inclusion criteria for the PSUR. Of the 432 reports included in this PSUR, 366 were initial reports and 66 were follow-up. Three hundred eleven (311) or 72% were from the US. Forty eight (48) of the 311 US cases originated from US litigation report sources; 20 initial and 28 follow-up reports. All but 8 of the US litigation cases (40) contained at least one event consistent with drug abuse, drug dependence, drug addiction, withdrawal and/or overdose. Of the overall total of 432 cases, a fatal outcome was reported in 97 cases. Overdose was reported in 69 of the 432 cases, 50 of which were fatal. Drug abuse, drug dependence, drug addiction and/or withdrawal were reported in 206 of the 432 cases, 42 of which were associated with a fatal outcome.

The reports received during this PSUR reporting period are similar in nature to those described previously, and include well-known pharmacological effects of opioids as discussed in the oxycodone CCDS or events that occur commonly in the oxycodone-using population, but with no reasonable causal association with oxycodone. The most significant safety issues for oxycodone remain abuse, dependence, and overdose, although these occurrences are almost exclusive to the USA. The MAH will continue to closely monitor international safety reports, suspected interactions between oxycodone and other drugs, and cases involving hepatic dysfunction, sequelae of constipation, aggression, tooth disorders, potential interactions with proton pump inhibitors, and prolongation of the QTc interval.

The oxycodone CCDS was revised as of 07August 2009 to include 2 additional preferred terms (cholestasis and dental caries) in Section 4.8 Undesirable Effects and updated text regarding the co-administration of oxycodone with drugs that inhibit or induce CYP2D6 and CYP3A4 pathways in Section 4.5 Drug Interactions. Additionally, updates were made to narratives covering Teratogenicity and Mutagenicity in the Preclinical Safety Information Section 5.3 as well as various reference changes. No additional changes to the product safety information are warranted at this point in time based on the information contained in this report, which reaffirms the favorable benefit-risk balance for oxycodone when used in accordance with the instructions given in the CCDS.

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Periodic Safety Update Report

1. INTRODUCTION

Oxycodone is a semi synthetic opioid derived from the opium alkaloid, thebaine. Oxycodone shares certain physicochemical characteristics, and opioid receptor agonist activity, with morphine and other similar opioids. The principal pharmacological actions are analgesia, and effects on the central nervous system and smooth muscle. Oxycodone is controlled internationally under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Oxycodone has been used as an analgesic for over 80 years, particularly in the USA, where it has been incorporated in a variety of combination preparations. Oxycodone became more widely used in the 1960's with the introduction of Percodan® and Percocet®, which are combination preparations with aspirin and paracetamol, respectively. In 1995 the oral oxycodone modified-release formulation, OxyContin® Tablets, was introduced in the USA. OxyContin has subsequently been registered in many countries throughout Europe, Asia, South America and Australia.

Oxycodone is available in immediate-release and controlled-release oral preparations and in parenteral formulations, and is manufactured and marketed globally by, among others, the Purdue/Mundipharma/Napp independent associated companies. In the third quarter of 2005, Purdue Pharma L.P. made generic oxycodone hydrochloride CR Tablets 10 mg, 20 mg, 40 mg and 80 mg commercially available and authorized the distribution by a third party distributor under the approved NDA #20-553. As of 28 February 2007, Purdue Pharma no longer distributes or markets generic oxycodone.

This report has been prepared in accordance with ICH guidelines on "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (CPMP/ICH/288/95) in brief named ICH E2C and later modified by an Addendum to ICH E2C – final document name ICH E2C(R). ICH E2C(R) was later published in the form of "Volume 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use (Sep 2008)," the requirement of which were also considered in preparing this PSUR.

Following preparation of the June 2009 PSUR, it was noted that some minor amendments were required. Please see Appendix IXd for more information.

The data lock point for this report was 12 October 2009.

2. WORLDWIDE MARKET AUTHORIZATION STATUS

OxyContin Tablets were first registered on 12 December 1995 in the United States and launched for marketing on 18 December 1995. Since then oxycodone has been registered in a number of countries worldwide. A summary of the worldwide marketing authorization status together with the licensed indications and local trademarks is included in Appendix I.

During the reporting interval (13 April 2009 - 12 October 2009) the following licenses were approved:

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication	Dosing Frequency
Belgium	OxyContin 10 mg/ml, oplossing voor injectie (1 ml & 2 ml)	21-Apr-09	Not marketed	09-Jan-12	Severe to most severe pain	q4-6h
	OxyContin 50 mg/ml, oplossing voor injectie	04-Sep-09	Not marketed	29-May-12	Severe to most severe pain	q4-6h
	OxyContin 15, 30, 60, 120 & 160 mg	07-Oct-09	Not marketed	06-Nov-13	Severe to most severe pain.	q12h
Germany	Oxygesic Dispersa 5, 10 & 20 mg	26-May-09	Not marketed	21-Dec-12	Severe to most severe pain.	q4-6h
Luxembourg	OxyContin 10 mg/ml oplossing voor injectie	10-Aug-09	Not marketed	09-Jan-12	Severe to most severe pain.	q4-6h
New Zealand	OxyContin tablet 15 & 30 mg	09-Jul-09	Not launched	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia	Q12h
Panama	OxyContin 20mg tablets	15-Jul-09	Not Marketed	15-Jul-15	Moderate to severe pain where use of an opioid is appropriate for more than a few days	Q12h
Philippines	OxyNorm Injection	31-Jul-09	Not marketed	31-Jul-12	For the treatment of	i.v. (Bolus): Dilute to 1 mg/mL in

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication	Dosing Frequency
	10mg/mL				moderate to severe pain in patients with cancer and post-operative pain; for the treatment of severe pain requiring the use of strong opioids.	0.9% saline, 5% dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over 1-2 minutes. Doses should not be administered more frequently than every 4 hours i.v. (Infusion): Dilute to 1 mg/mL in 0.9% saline, 5% dextrose or water for injections. A starting dose of 2 mg/hour is recommended

[1] No renewal process

The following Marketing Authorization was approved in Argentina during a previous report interval, but had not been previously reported in the global PSUR.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication	Dosing Frequency
Argentina	OxyRapid Capsules 10 & 20 mg	30-Mar-09	Not Marketed	30-Mar14	Relief of moderate to moderately severe pain	Q4-6h

During this reporting interval there was one (1) application rejected in Denmark for OxyNorm (50 mg/ml solution for injection and infusion) on 03JUL2009. The Danish Health Authority did not consider that the oxycodone hydrochloride aldol dimer had been qualified at daily doses in excess of 100 mg.

During the reporting interval (13 April 2009 – 12 October 2009) no licenses were withdrawn or allowed to expired.

3. UPDATE OF REGULATORY AUTHORITY OR MAH ACTIONS TAKEN FOR SAFETY REASONS

There were a total of nine (9) Marketing Authorization Holder Actions taken for safety reasons during the reporting interval (13 April 2009 – 12 October 2009); one (1) in Austria, two (2) in Canada, one (1) in China, two (2) in the Republic of Ireland, two (2) in Spain, and one (1) in the United States.

Country	Authorised Product Name	Action taken	Additional documentation to be supplied (Y/N)
Austria	OxyNorm 5, 10 & 20 mg IR Oral capsules	May-09: Submission of variation to update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.3 of the SmPC to bring it in line with the CCDS dated 29 November 2007.	N
Canada	OxyContin (oxycodone HCl controlled release tablets) 5, 10, 15, 20, 30, 40, 60, 80, 120, 160 mg Oxy•IR (oxycodone HCl tablets) 5, 10, 20 mg	27-Aug-09: Approval received for the 16-JUN-09 S/NDS filed regarding revisions to "Dose Titration", related to dose optimization and to the established sentence on breakthrough pain. Also, consistent with US Prescribing Information, the statement regarding achievement of steady-state was updated from 24 hours, to 24-36 hours, of initiation of dosing and the statement regarding ambulatory and postoperative use was revised to a more succinct statement to guide use.	N
China	OXYCONTIN tablets (oxycodone hydrochloride prolonged-release	During renewal of the MA, SFDA (State Food and Drug Administration) requested the Chinese leaflet of OXYCONTIN to be amended to	N

Country	Authorised Product Name	Action taken	Additional documentation to be supplied (Y/N)
	tablets)	include warning about potential for drug abuse & addiction.	
Republic of Ireland	OxyNorm 1mg/ml & 10 mg/ml IR Oral Liquid	May-09: Submission of variation to update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.3 of the SmPC to bring it in line with the CCDS dated 29 November 2007.	N
	OxyNorm 5, 10 & 20 mg IR Oral capsules	May-09: Submission of variation to update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.3 of the SmPC to bring it in line with the CCDS dated 29 November 2007.	N
Spain	OxyNorm 1mg/ml & 10 mg/ml IR Oral Liquid	May-09: Submission of variation to update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.3 of the SmPC to bring it in line with the CCDS dated 29 November 2007.	N
	OxyNorm 5, 10 & 20 mg IR Oral capsules	May-09: Submission of variation to update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.3 of the SmPC to bring it in line with the CCDS dated 29 November 2007.	N
US	OxyContin Tablets	The following sections of the package insert have been revised to update information regarding CYP3A and CYP2D6 mediated metabolic pathways and potential drug interactions with inhibitors and inducers of CYP3A4 and CYP2D6: PHARMACOKINETICS AND METABOLISM: Metabolism and Drug-Drug Interactions; PRECAUTIONS: Drug-Drug Interactions.	N

4. CHANGES TO REFERENCE SAFETY INFORMATION

The Oxycodone Company Core Data Sheet (CCDS) was revised as of 07August 2009 and was used to reference listedness for this PSUR. This document can be found in Appendix III. Revisions include changes to the following sections and various updates to the references.

- **Section 4.5 Drug Interactions**
  - Updated to include revised text regarding the CYP2D6 and CYP3A4 pathways.

  Previous text:
  Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. While these pathways may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.

  Revision:
  Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly.

- **Section 4.8 Undesirable Effects:**
  - Two (2) additional Adverse Events cholestasis (uncommon) and dental caries (uncommon) were added.
  - Existing term "*Asthenia*" updated to "*Asthenic Conditions*" following a MedDRA analysis.
  - Existing term "*Increased Hepatic Enzymes*" was reassigned to the Hepatobiliary Disorders SOC (previously captured under Investigations SOC).

- **Section 5.3 Preclinical Safety Information:**
  - Updated text and references for Section 5.3.1 Teratogenicity and Section 5.3.3 Mutagenicity

  5.3.1 Teratogenicity

  Previous text:
  The effect of oxycodone in human reproduction has not been adequately studied. No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult human dose of 160 mg/day respectively, did not reveal evidence of harm to the fetus due to oxycodone.

  Revision:
  Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27)

presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioral and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

5.3.3 Mutagenicity

Previous text:
Data from several studies indicate that the genotoxic risk of oxycodone to humans may be considered low. Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at doses of up to1500 μg/ml, and with activation after 48 hours of exposure at doses up to 5000 μg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 μg/ml).

Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/ml or greater with metabolic activation and at 400 μg/ml or greater without metabolic activation.

Revision:
The results of in vitro and in vivo studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an in vivo micronucleus assay in the mouse. Oxycodone produced a positive response in the in vitro mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two in vitro chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at 48 hours after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

5. PATIENT EXPOSURE

Appendix IV contains a listing of the units sold during the period 01 Jan 2009 to 30 Jun 2009. The largest number of units sold over this reporting interval was in the United States of America. The variance between different countries reflects not only the population of the country but also the medical pattern of use and the time since the launch of the preparation. This market estimate of patient exposure may be inherently low due to use of generic and competitive products.

The exposure figures were estimated on the basis of 2 doses per day for the modified release preparations, 4 doses per day for the normal release preparations, and 6 doses per day for the OxyNorm® Injections. The number of patient days treatment for each strength, for each pack size, and for each country was then calculated. Taking a conservative approach, the summation provides an estimate of the number of "patient days" exposure. The total "patient days" of exposure was 215,553,691 (7,184,456 patient months) for the modified release preparations; 18,374,065 (612,469 patient months) for the normal release preparations; and, 488,973 (16,299 patient months) for the OxyNorm Injections preparations. This equates to 7,813,224 patient months of exposure within the six months referenced (01 Jan 2009 to 30 Jun 2009).

6. PRESENTATION OF INDIVIDUAL CASE HISTORIES

6.1. Presentation of the Line Listings

The individual cases included in this report have been categorized according to "Volume 9A of The Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use (Sep 2008)". Line listings and summary tabulations have been run as specified in the guidelines above, and include the following:

Appendix Va	A line listing of all cases within the reporting interval considered related and were received from Healthcare Professionals (HCPs), which have been classified as serious, and listed or unlisted against the CCDS, or were non-serious and unlisted.
Appendix Vb	Summary Tabulation of all adverse event (AE) data from within the line listing above (Appendix Va)
Appendix Vc	Summary Tabulation of all non-legal cases from within the line listing above (Appendix Va)
Appendix Vd	Summary Tabulation for all legal cases from within the line listing above (Appendix Va)

The line listing in Appendix Va is presented by MedDRA® (version 12.0) System Organ Class (SOC) of the primary adverse event (AE) term. In cases with more than one adverse event, the primary event is usually the most serious event as judged by the marketing authorization holder. The summary tabulation in Appendix Vb contains all adverse events in the cases from the line

listing, separated by seriousness and listedness of the event. Appendix Vc and Vd further divide the summary tabulation of adverse events by non-legal and legal report sources, respectively.

6.2. MAH Analysis of Individual Case Histories

During this reporting period (13 April 2009 – 12 October 2009), the Drug Safety and Pharmacovigilance Group received or created a total of 2,394 cases, initial and follow-up reports, from worldwide sources involving an oxycodone hydrochloride-containing product ("oxycodone"). Of these, 432 cases (366 initial and 66 follow-up cases) met criteria for inclusion in this PSUR.

Tables I and II present the cases by country of incidence and by report source. As shown on Table 1, the country of incidence for the majority of reports was the USA (72%), followed by France and the United Kingdom each at (5%).

Table I: Cases by Country of Incidence

Country	Number of cases
United States	311
France	22
United Kingdom	22
Germany	12
Netherlands	11
Canada	10
Japan	10
Australia	9
New Zealand	6
Italy	5
Ireland	3
Sweden	3
Switzerland	2
Belgium	2
Finland	2
China	1
Spain	1
Total	**432**

As shown in Table II, most of the reports were received from spontaneous sources (N=340) followed by regulatory authority sources (N=34). Of note, if you add up contributions from post-marketing, clinical trial, and non-company studies, the total of all studies is 54.

Table II: Cases by report source

Report Source	Number of cases
Spontaneous*	340
Regulatory Authority	34
Literature	3
Post-marketing study**	34
Clinical Trial	3
Non-company study	17
Other	1
Total	**432**

* Includes US legal reports
** Includes reports from IPAP (Purdue's Individual Patient Assistance Program)

The tables below summarize the case totals broken down by seriousness and listedness.

Table III: Cases by Seriousness, Listedness

	Serious	Non-serious	Total
Unlisted	126	51	177
Listed	255	0	255
Total	**381**	**51**	**432**

The 432 cases in this report included 381 serious and 51 non-serious cases. Of the 381 serious cases, 126 were unlisted, and of the 51 non-serious cases, all were unlisted. A fatal outcome was reported in 97 of the 432 cases.

The summary tabulation of the 432 cases (Appendix Vb) included 1,268 adverse events. The SOCs with the most number of events were the Psychiatric disorders SOC (N = 468) the General disorders SOC (N = 219) and the Injury, poisoning and procedural complications SOC (N = 140); see Table IV below.

Table IV
Adverse Events by SOC, Seriousness, and Listedness

SOC	Non-Serious		Serious		Total
	Listed	Unlisted	Listed	Unlisted	
Blood and lymphatic system disorders	0	3	0	3	6
Cardiac disorders	1	1	3	11	16
Eye disorders	4	1	1	1	7
Gastrointestinal disorders	38	7	37	18	100
General disorders and administration site conditions	89	75	26	29	219
Hepatobiliary disorders	0	1	1	2	4
Immune system disorders	0	1	2	0	3
Infections and infestations	0	6	0	18	24
Injury, poisoning and procedural complications	28	10	86	16	140
Investigations	1	5	6	3	15
Metabolism and nutrition disorders	4	6	4	7	21
Musculoskeletal and connective tissue disorders	1	9	1	3	14
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	0	0	0	5	5
Nervous system disorders	35	7	40	16	98
Pregnancy, puerperium and perinatal condition	0	0	0	2	2
Psychiatric disorders	107	77	249	35	468
Renal and urinary disorders	1	5	4	3	13
Reproductive system and breast disorders	0	3	0	2	5
Respiratory, thoracic and mediastinal disorders	4	4	19	10	37
Skin and subcutaneous tissue disorders	13	3	10	4	30
Social circumstances	2	6	5	3	16
Surgical and medical procedures	0	0	9	4	13

Table IV Adverse Events by SOC, Seriousness, and Listedness					
SOC	Non-Serious		Serious		Total
	Listed	Unlisted	Listed	Unlisted	
Vascular disorders	0	4	3	5	12
Total	**328**	**234**	**506**	**200**	**1,268**

Oxycodone is available in immediate and controlled-release oral formulations, and for intravenous use. The vast majority of cases involved controlled-release oral formulations as a suspect drug. Sixteen (16) cases involved an immediate release formulation as a suspect drug without a controlled-release formulation as an additional co-suspect. Primary events for the oral immediate release formulations included the following: drug effect increased; drug withdrawal syndrome, neonatal; fatigue; overdose; blood alkaline phosphatase increased; malignant neoplasm progression; myoclonus; drug abuse; drug dependence; pharyngeal edema; blister; rash macula-papular; and, pain management. There were also 2 cases involving intravenous formulations with primary events of accidental overdose and respiratory distress, and 1 case involving a liquid formulation with a primary event of drug dependence. Due to the small number of cases, an analysis of the safety profile of immediate release formulations as compared to controlled release formulations, and IV formulations compared to oral formulations, is difficult. However, the adverse events reported in these few cases suggest that the overall safety profile of the immediate release and IV formulations appears to be similar to that of reports with controlled release formulations.

6.3. Legal Cases

Forty-eight (48) of the 432 cases in this PSUR originated from report sources related to US litigation; 20 initial and 28 follow-up cases. Nineteen of 48 cases were associated with a fatal outcome. Forty (40) of the 48 litigation cases contained at least one event consistent with drug abuse, drug dependence, drug addiction, withdrawal and/or overdose. Fourteen (14) of the 48 cases involved an overdose term. Eleven (11) of the 14 overdose cases were associated with a fatal outcome. The remaining 8 fatal cases involved the following primary events: drug dependence (3); sepsis (2); arteriosclerosis, coronary artery; non-small cell lung cancer; and, completed suicide.

Events arising from such legal cases may not have the same significance as those arising from "usual" spontaneous cases, since these events are typically not reported by the prescribing healthcare professional, and since most cases contain little specific information with which to medically assess event causality. Throughout this document, cases from legal sources are included in tabulation tables, and are addressed in narratives when relevant. The medical review of the legal cases did not identify any new issues attributable to oxycodone.

6.4. Individual Case Presentation

Cases relevant to ongoing surveillance activities (e.g. serious hepatic function disorders, serious sequelae of constipation, tooth disorders) and those involving specific areas such as medication errors, paediatrics, and labor and delivery are discussed in section 9. The remaining serious unlisted cases that were fatal or deserve individual discussion due to medical significance of the case are presented as narratives in the section below, by system organ class (SOC) of the primary event term.

Cardiac Disorders

GBR-2009-0005639 (cardiac arrhythmia) involved a male patient (date of birth 01Nov52), with concurrent conditions that included low back pain, chronic sciatica, depression, excessive alcohol use, muscle pain, tremor, and a history of smoking. Concomitant medications included diazepam, propanolol and Prothiaden® (dosulepin). The patient was switched from Depronal® (dextropropoxyphene hydrochloride) to OxyContin 5 mg twice daily. During the first week of treatment with OxyContin the patient reported to his physician that he was experiencing mild headache. Ten days after switching to OxyContin the patient died. The physician suspected that the patient died from a cardiac arrhythmia, possibly related to treatment with OxyContin. No further details provided.

MAH Comment: Based on compatible chronology, a contributory role of oxycodone cannot be excluded. However, additional information, including the results of an autopsy, if done, and historical information regarding the presence of underlying cardiac disease and the indication for propanolol is necessary for a proper medical assessment. The patient's excessive alcohol use and concomitant therapy with a tricyclic antidepressant (Prothiaden®) may have contributed to the occurrence of the suspected arrhythmia. Alcohol abuse is known to be associated with a number of cardiac arrhythmias and an increased risk of sudden death, and, according to one study, the use of higher-dose tricyclic antidepressants (TCAs) was also associated with an increased risk of sudden cardiac death.[1] The patient's history of smoking also increases his risk for cardiovascular disease.

GBR-2009-0005202 (bradycardia) was received via a regulatory authority in Italy and involves a female patient of unreported age who reported vomiting, nausea, shivers and dizziness after taking OxyContin 10mg for sciatica. The patient was noted to have hypotension and bradycardia in the ambulance and was diagnosed with "vasovagal syncope" secondary to pain and opioid therapy.

***MAH Comment*:** Based on a positive temporal association to oxycodone therapy, a contribution (by oxycodone) to this patient's events cannot be excluded. Nausea, vomiting, tremor, hypotension, and syncope are all listed events for oxycodone. These events may have led to the apparent vasovagal reaction and bradycardia.

MAG-2009-0001070 (cardiorespiratory arrest) involved a female patient with metastatic colon cancer who was enrolled in a clinical study of oxycodone hydrochloride hydrate (S-811717),

[1] Micromedex Healthcare Series Drugdex Evaluations (online) dothiepin

protocol No. 0809V9131, and developed cardio-respiratory arrest after receiving S-811717 for the treatment of cancer pain. The patient started receiving the drug one day prior to death at a dose of 100mg/d IV. Rescue medication was given because of continuation of pain, sleepiness, queasiness, and vomiting. After developing a large quantity of black colored vomit, she lost consciousness, her breathing gradually slowed, and a respiratory arrest was noted. An autopsy was not performed. No further details provided.

***MAH Comment*:** Based on the positive temporal association to oxycodone therapy, a relationship between oxycodone and the cardiorespiratory arrest cannot be ruled out. However, the patient's underlying disease, end-stage carcinoma with metastasis and carcinomatous peritonitis, and the likely upper gastrointestinal bleeding (black colored vomit) likely contributed to the patient's reactions and ultimate demise.

DEU-2009-0005297 (myocardial infarction) involves a 73-year-old female who was enrolled in a Mundipharma sponsored clinical trial (OXN2001), a study to determine the safety and efficacy of oxycodone/naloxone (OXN) prolonged release tablets in subjects with moderate to severe, chronic cancer pain). The patient's current conditions included pulmonary cancer, bronchial cancer, hypertension and neuropathic pain. She had undergone radiation therapy and chemotherapy. Her concomitant medications included atenolol, hydrochlorothiazide/lisinopril, dexamethasone and pregabalin. Two weeks after initiating blinded study medication (OXN vs. oxycodone CR tabs) she experienced worsening dyspnea and leg edema requiring hospitalization. Study medication was discontinued as a result of the hospitalization. She received two therapeutic percutaneous punctures of the abdominal cavity, along with trofosamide, amitriptyline, metoclopramide and diuretics as corrective therapy with improvement of the ascites. The patient was re-hospitalized on 2 occasions for ongoing ascites. The patient expired during the third hospitalization due to myocardial infarction, 2 weeks after discontinuing study medication. The investigator found all events to be unlikely related to the treatment with the study medication.

MAH Comment: Peripheral edema and dyspnea are listed events for oxycodone therapy. However, the patient's underlying pulmonary carcinoma, which may be associated with peritoneal metastasis and malignant ascites, may serve as plausible alternative etiology for the patient's events. The patient's advanced age and hypertensive cardiovascular disease may serve as a more likely alternative etiology for the fatal MI, which occurred 2 weeks after study drug discontinuation.

GBR-2009-0005558 (myocardial infarction) involved a 75 or 77-year-male with a history of colon neoplasm, spinal compression, hypercholesterolemia and hypertension who had been treated with OxyContin and experienced an asymptomatic myocardial infarction, which reportedly led to delayed management. The physician did not attribute the myocardial infarction to oxycodone therapy, but believed that the oxycodone may have masked the symptoms, delaying management, possibly contributing to the fatal outcome.

MAH Comment: The patient's underlying risk factors may serve as a more plausible alternative explanation for the patient's events. Silent myocardial infarctions occur outside opiate therapy, particularly in elderly patients and diabetic patients. Therefore, it is hard to determine the role, if any, oxycodone played in masking the patient's symptom.

USA-2006-0026059 (myocardial infarction), reported in the previous PSUR, involves a 74-year-old male with a history of triple bypass surgery (1990), MI (2003) and post traumatic stress disorder (PTSD) who was treated with OxyContin® following a car accident. Concomitant medications included pantoprazole, lorazepam and an unspecified "thyroid medication." An unspecified period of time after initiating oxycodone he experienced stomach pain, stomach irritation, weight loss, difficulty gaining weight, increased insomnia, paranoia and decreased pain relief from oxycodone (becoming tolerant). In DEC2006, he experienced a second MI. The additional information revealed that the patient had an endoscopy and colonoscopy in Aug2009 and was diagnosed with colitis. The patient's colitis treatment medication included budenoside.

MAH comment: There is insufficient information to assess the relationship between the MI and therapy with oxycodone. The patient's underlying cardiovascular disease (triple bypass surgery in 1990, MI in 2003) and his advanced age may serve as a plausible alternative explanation for the patient's MI.

MAG-2009-0000790 (sinus bradycardia) concerns a 75-year-old male who presented with pain due to hepatocellular carcinoma and received OxyContin (10 mg/d) and prochloperazine (15 mg/d). The following day, his pulse rate was in the 30 per minute range and electrocardiogram (ECG) revealed sinus bradycardia with heart rate of 38. OxyContin and Novamin were discontinued. Carvedilol was discontinued the day after and his heart rate returned to the 50 per minute range (bradycardia resolved) within one day. The reporting physician considered the bradycardia possibly related to the oxycodone or carvedilol.

MAH Comment: Based on a positive temporal association to oxycodone therapy, a possible contribution cannot be excluded. However, the bradycardia is most probably related to the beta-blocker carvedilol, particularly given the positive dechallenge.

Eye Disorders

USA 2009-0039778 (blindness) involved a 24-year-old female taking dalteparim, Diclofenac and paracetamol who had been treated with oxycodone hydrochloride (total dose 70mg) for 2 days and experienced loss of vision, confused speech, and was delirious when she woke up after a lower uterine segment caesarean section. An MRI was normal. The patient recovered 2 days later.

MAH Comment: There is insufficient information to assess the relationship between these events and therapy with oxycodone. Additional information, such as details of the operative course, anesthetics used, history of thrombotic events, and the indication for heparin therapy, would be important for a proper medical assessment. Of note, abnormal vision, speech disorder, confusional state, agitation, thinking abnormal, and hallucinations are all listed events for oxycodone. Additionally, the CCDS states that for controlled release products, oxycodone is not recommended for pre-operative use or within the first 12-24 hours post-operatively. For immediate release products, oxycodone should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

Gastrointestinal Disorders

USA-2009-0037870 (oesophageal oedema) involved a female patient who developed esophageal swelling, difficulty breathing, and blurred vision after taking OxyContin 15 mg.

MAH Comment: There is insufficient information to assess the relationship between oxycodone and the patient's symptoms. Anaphylactic reactions, anaphylactoid reactions, hypersensitivity, dyspnea, and abnormal vision are listed events for oxycodone. Additional information would be necessary for a proper medical assessment.

GBR-2009-0005218 (ischemic colitis) involved a 62-year-old male with a history of hypertension and osteoporosis who was taking oral oxycodone hydrochloride (modified release) for vertebral collapse. Treatment was started on 29DEC2008 at 160 mg twice daily. On 02APR2009 the patient experienced ischemic colitis, which resolved that same day. The oxycodone dose was not changed. The surgical team treating the patient reportedly gave patient the impression that they felt oxycodone could have been implicated in the colitis.

MAH Comment: There is insufficient information to confirm the diagnosis of ischemic colitis and to assess the causal role of oxycodone, if any. Additional information such as the diagnostic and laboratory investigations conducted would be important for a proper medical assessment.

Infections and Infestations

USA-2009-0038347 (cardiac infection) involved a male patient (age unspecified) who was hospitalized with a cardiac abscess after injecting OxyContin. The physician did not indicate that the patient had been prescribed OxyContin or other details of the events. The outcome of the events was unknown.

USA-2009-0040411 (sepsis) involved a male patient of unspecified age on clonidine who presented to the hospital with sepsis. Reportedly, the patient was crushing the OxyContin and the clonidine.

MAH Comment: The latter 2 cases of cardiac abscess and sepsis can be attributed to known complications of intravenous drug abuse.

USA-2009-0037298 (sepsis) was initially received via US litigation sources and involved a female patient with a history of hypertension, diabetes mellitus, depression, peptic ulcer disease, cholecystectomy, spinal stenosis, and degenerative joint disease on long term OxyContin therapy. On 29JUN2007, the patient was transferred from a local hospital to a medical center after being treated for ischemic colitis and C. difficile colitis. She was admitted for abdominal pain, nausea, vomiting and diarrhea with bloody stools. An esophagogastroduodenoscopy was performed and the patient was found to have a large gastric ulcer. The patient developed hypotension, upper gastrointestinal bleed, fever, and mental status changes. She was diagnosed with possible septic

shock and treated with antibiotics. A blood culture was positive for Acinetobacter bacteremia and fungemia. The patient subsequently expired. The autopsy showed evidence of hypertensive and atherosclerotic cardiovascular disease, congestive heart failure, several sites of infection including probable diffuse colitis (differential diagnosis: ischemic colitis vs. pseudomembranous colitis), left lung early bronchopneumonia, bilateral kidneys with micro abscesses, and left lower leg skin ulceration with inflammation. The patient was thought to have autonomic dysfunction of bowel likely secondary to narcotic usage. The cause of death was reported to be sepsis with related multi-organ failure; with hypertensive and atherosclerotic cardiovascular as contributing factors.

MAH Comment: Based on the available data (i.e. C. difficile colitis treated with antibiotic therapy, fever, and positive blood cultures for Acinetobacter bacteremia and fungemia), an infectious etiology is the most probable explanation for the colitis, septic shock and the patient's ultimate demise.

GBR-2009-0005339 (infection) was received from an investigator in the Netherlands and involved a male patient of unspecified age involved in a non-company, non-interventional study of neuropathic pain. The patient's concomitant medications included paroxetine 20 mg, amitriptyline 25 mg, ascal 100 mg, lipitor 40 mg and metoprolol 100 mg, all for unspecified indications. Treatment with OxyContin 5 mg twice daily for neuropathic pain was initiated on 07Mar2008 and withdrawn on 06May2008. During the study the patient experienced a severe infection. It is not known if the patient recovered.

MAH Comment: There is insufficient information to assess the relationship between the event and use of oxycodone.

MAG-2009-0001060 (acute pneumonia) involved a 78-year-old male participating in a non-interventional study involving Sutent® (sunitinib maleate) for metastatic renal cell carcinoma who was treated with OxyContin 10mg twice daily. Concomitant medications included meloxicam, allopurinol, atenolol, amlodipine, acetylsalicylic acid (ASA), pantethine, prochlorperazine, metoclopramide, and Interferon® (INF-Alfa). The patient developed disturbed consciousness (grade 4), respiratory arrest (grade 4), hyponatraemia (grade 4), acute pneumonia (grade 3) paralysis of legs, (grade 4) and pancytopenia (grade 3), and sunitinib was discontinued. The patient recovered from the pancytopenia, acute pneumonia, and consciousness disturbed, but the leg paralysis still persisted at the time of last contact. The investigator assessed the pancytopenia as definitely related to sunitinib; the disturbed consciousness and respiratory arrest as probably related to sunitinib and OxyContin; the event of hyponatraemia as probably related to sunitinib; the event of acute pneumonia, which was considered to be due to the artificial respirator, and the paralysis as not related to sunitinib.

MAH Comment: Based on the available information, the causal / contributory role of oxycodone in the occurrence of the respiratory arrest and consciousness disturbed cannot be excluded. However, as noted by the investigator, Sutent, the patient's underlying metastatic renal cell carcinoma and the artificial respirator, may serve as more likely alternative explanations for the occurrence of the pancytopenia, pneumonia and the other events.

Injury, Poisoning and Procedural Complications

GBR-2009-0005593 (overdose) involved a male patient around 60 with a history of renal cancer status post bilateral nephrectomy on dialysis for 4-5 years and a recent morphine overdose who had been treated with OxyNorm for pain secondary to bone metastases and experienced an overdose associated with confusion and a behavior disorder, threw himself out of the window and died. During a dialysis session the nurse observed overdose symptoms with somnolence and confusion but no respiratory depression. OxyNorm was stopped and Narcan was given. The following day the patient presented with excessive sedation and miosis but no respiratory depression and another dialysis was performed. His condition remained unchanged a cerebral scan was performed, which excluded cerebral metastases. Lab tests showed hypercalcemia, which was treated. The patient subsequently became agitated and restraints were used. A few days later, during a brief pause in the restraints, the patient, still very agitated and confused, threw himself out of the window and died. The physician indicated that the patient did not present with depression and excluded a suicidal motivation.

MAH Comment: Based on the available information, a contributory role of oxycodone cannot be ruled out. However, as suggested by the physician, the event was likely multifactorial, associated with the underlying cancer, chronic pain due to bone metastases, years of dialysis therapy, hypercalcemia, and the patient's concomitant medications, which contributed to the behavioral abnormalities. The oxycodone CCDS states that caution must be exercised when administering oxycodone to the debilitated elderly or infirm and those -/with severely impaired renal function. Confusional state, thinking abnormal, agitation, and affect lability are listed events for oxycodone.

Investigations

USA-2009-0039014 (weight increased) involved a 57-year-old female with metastatic cervical cancer, diabetes and hypertension who had been treated with OxyContin 40 mg twice daily and experienced increased weight (66 pounds) and increased lower extremity edema. An ultrasound revealed acute deep venous thrombosis (DVT) in left common femoral to profunda femoris and an abdominal/pelvic CT (computed tomography) revealed an enlarged left pelvic mass, possible obstruction of left iliac vasculature and marked subcutaneous edema. The physician believed the weight gain and edema were definitely related to OxyContin and discontinued therapy.

MAH Comment: Based on the compatible chronology, a contributory role of oxycodone therapy cannot be excluded. Edema and peripheral edema are listed events in the oxycodone CCDS. However, the patient's underlying carcinoma, the pelvic mass obstructing the left iliac vein, and the DVT may serve as a more likely, alternative explanation for the patient's events.

Metabolism and Nutrition Disorders

USA-2009-0038839 (cachexia) was received via Purdue's Individual Patient Assistance Program (IPAP) in the US and involved a 69-year-old male who had been taking OxyContin 20 mg every 12

hours from 2007 to 27JUN2009 for metastatic renal cell cancer. The patient died on 27JUN2009. The cause of death was reported as cachexia and pneumonia.

MAH Comment: The patient's cachexia, pneumonia and death are most likely due to his underlying metastatic renal cell cancer.

USA-2009-0039087 (hyperkalemia) involved a 66-year-old female with pre-existing renal disease who was started on oxycodone 220 mg for an unspecified indication. Concomitant medications included carbidopa, levodopa, cilazapril, olanzapine and valproate sodium. On the same day oxycodone was started, the patient experienced convulsions, decreased consciousness, hypotension, hyperkalemia and a medication error (dosage). Oxycodone dosage was decreased and the patient recovered without sequelae.

MAH Comment: Based on the positive temporal association between the events and initiation of oxycodone therapy, a causal relationship cannot be excluded. However, additional information including the patient's past medical history, prior history of seizures, the indication for valproate, and the details of the medication error (possible overdose), would be important for a proper medical assessment. Concomitant therapy with multiple CNS acting medications may have contributed to the occurrence of the decreased consciousness, and the patient's underlying renal disease may have contributed to the hyperkalemia. Of note, convulsions, hypotension and somnolence are all listed events in the oxycodone CCDS.

Musculoskeletal and Connective Tissue Disorders

GBR-2009-0005538 (osteoporotic fracture) involved a 47-year-old-male with lumbar pain and sciatica who experienced severe osteoporosis with fracture and hypovitaminosis D (refractory to corrective treatment with injectable vitamin D) after 8-9 years of therapy with OxyContin, OxyNorm, and gabapentin. Gabapentin was stopped for one year, and no improvement of osteoporosis was noted. Corrective treatment for the osteoporosis and hypovitaminosis consisted of calcium carbonate and ergocalciferol. At the time of last contact, the patient had not yet recovered.

MAH Comment: There is insufficient information to assess the relationship between the events of this case and drug therapy with oxycodone. Additional information, including the etiological and diagnostic evaluation of the refractory hypovitaminosis D, would be important for a proper assessment. Of note, osteoporosis can be caused by hypovitaminosis D (due to hypocalcemia). Furthermore, the occurrence of hypovitaminosis D and osteoporosis in a relatively healthy young adult male suggests a pre-existing, underlying endocrinological disease (e.g. hyperparathyroidism) or a malabsorptive disorder (e.g. celiac disease).

Nervous System Disorders

USA 2009-0039222 (ataxia) involved a 52-year-old male with a history of osteomyelitis who had been treated with OxyContin 20mg daily for "other disturbance of sensation." Additional suspect medications included: Endone® (immediate-release oxycodone), cefalotin sodium, omeprazole

and vancomycin. Concomitant medications included lincomycin and temazepam. About 10 days after OxyContin was initiated, the patient experienced visual hallucinations. OxyContin was subsequently discontinued. Five days after OxyContin discontinuation, the patient developed worsening visual hallucinations, ataxia and dysarthria and all additional suspect medications were discontinued. The patient was switched to Ampicillin following PCN desensitization and recovered.

MAH Comment: Based on compatible chronology, a contributory role of oxycodone cannot be excluded. However, the patient's underlying infection and the multiple co-suspect medications may have contributed to his events. Of note, hallucinations and speech disorder are listed terms in the oxycodone CCDS.

USA-2009-0039540 (coma) refers to a male patient of unspecified age with a history of a failed laminectomy procedure who was taking OxyContin for pain (120 mg every 8 hours). The patient's dose was increased to 160 mg every 8 hours due to escalating pain and the patient became comatose.

MAH Comment: Based on the available information, the causal role of oxycodone in the occurrence of the coma cannot be excluded. Somnolence is a listed event in the oxycodone CCDS and somnolence progressing to stupor or coma is listed for overdosage. Additional information such as the patient's age, medical history and the presence of renal / hepatic impairment would be important for a proper medical assessment.

USA-2009-0038466 (hyperesthesia) was received via a literature report:

> Garuba, M, Mostek DE, Burke WJ, Opioid-induced hyperalgesia in a patient with dementia. Journal of the American Geriatrics Society. 2009, Apr; 57 (4):748-749.

The report involved a female patient of undisclosed age with a complex pain syndrome for several years who developed opioid-induced hyperalgesia following increasing doses of oxycodone. Sixteen months prior to presentation she began receiving OxyContin and in the weeks preceding presentation her dosages of oxycodone and OxyContin were increased due to increasing pain. She presented with a chief complaint of pain all over her body and reportedly spent most of her day moaning with little sleep, agitation and restlessness. She had behavioral disturbances and she appeared to be in extreme misery and tortured by pain. At this time she was receiving OxyContin 10 mg tablets 3-4 times daily and at least 10 oxycodone 5 mg tablets as needed. Concomitant medications included trazodone, memantine, lorazepam, quetiapine and paracetamol. Opioid-induced hyperalgesia was suspected and oxycodone was tapered. Trazodone and memantine were discontinued, and quetiapine was gradually increased. Due to continued misery she was admitted and all narcotic pain medications were tapered. On discharge she had no pain except for mild hip pain and has only required scheduled paracetamol dosages.

MAH Comment: Based on the available information, the causal role of oxycodone cannot be excluded. The patient's multiple CNS acting concomitant medications may have contributed to the agitation, restlessness and behavioral disturbances.

GBR-2009-0005198 (myoclonus) involved a 35-year-female with a history of celiac disease, peripheral blood stem cell autograft, allogenic bone marrow transplantation and ileostomy who experienced hallucinations, myoclonus, transient consciousness disturbance and shakiness while receiving ketamine, OxyNorm, nefopam, chlorpromazine and cyclosporine. All of the suspect medications were withdrawn and the symptoms improved. Fentanyl was initiated for pain management, ketamine and chlorpromazine were reintroduced, and the confusional syndrome recurred. Cerebral MRI revealed spontaneous T1 hypersignal of the globus pallidus (which could reflect an underlying chronic hepatopathy) and an infiltration and thickening of the pituitary stalk compatible with a lymphomatous infiltration. The patient expired the following month due to worsening of the digestive lymphoma.

MAH Comment: Based on the positive temporal association, a contributory role of oxycodone in the occurrence of the patient's events cannot be excluded. Confusional state, agitation, hallucinations, muscle contractions involuntary and tremor are listed events in the oxycodone CCDS. The patient's underlying disease and multiple medications may have contributed to the events. Ketamine and chlorpromazine, both known to be associated with neuromuscular adverse events, may serve as plausible alternative explanations for the patient's events, particularly given the reoccurrence of the "confusional syndrome" following the re-initiation of these drugs.

GBR-2009-0005508 (myoclonus) involved a 39-year-old male with a history of severe angiitis (Churg Strauss syndrome) with respiratory failure, multi-neuritis, diabetes and hypertension who experienced paresthesia and myoclonus 7 months after initiating OxyContin LP (oxycodone), OxyNorm and Versatis® (lidocaine). The reactions persisted and it was proposed to discontinue the Versatis, OxyContin and OxyNorm and reintroduce Skenan LP and Actiskenen.

MAH Comment: Based on compatible chronology, a contributory role of oxycodone cannot be excluded. Muscle contractions involuntary and paresthesia are listed events in the oxycodone CCDS. The patient's underlying diabetes and multi-neuritis may have contributed to the occurrence of the events.

USA-2009-0037885 (myoclonus) involved an elderly female who experienced myoclonic jerks while taking OxyContin. No further details provided.

MAH Comment: There was insufficient information to assess the causal relationship between oxycodone and the myoclonus. Additional information including the patient's medical history, indication for OxyContin and concomitant medications would be necessary for a proper medical assessment.

GBR-2009-0005544 (paresis) involves a female patient taking OxyContin 5mg for pain. After a few days of therapy, approximately 30 minutes after OxyContin administration, the patient complained of paresis of her face and a swallowing disorder, which resolved after an unspecified period of time. OxyContin was continued as it provided good pain relief.

MAH Comment: Based on the positive temporal association to oxycodone therapy, a possible relationship to oxycodone therapy cannot be ruled out. However, without additional information such as the patient's age, underlying medical conditions and the clinical details surrounding the

event, a proper analysis is not possible. Of note, dysphagia is a listed event in the oxycodone CCDS.

USA-2009-0039097 (serotonin syndrome) involved a 56-year-old female with pre-existing renal and hepatic disease, hallucinations and recent surgery, who developed serotonin syndrome after an unspecified duration of therapy with OxyContin, OxyNorm, tramadol, ondansetron and fentanyl, all reported as suspect drugs. Concomitant medications included haloperidol. It was stated that dechallenge (no specific drugs(s) specified) resulted in definite improvement. There was no rechallenge and the patient recovered without sequelae.

MAH Comment: Tramadol, fentanyl, and ondansetron, all known to be associated with serotonin syndrome, may serve as plausible alternative explanations for the patient's events. The temporal information concerning the initiation of drug therapy in relation to the development of the serotonin syndrome and the details of the positive dechallenge would be important for a proper assessment.

Psychiatric Disorders

GBR-2009-0005354 (confusional state) involved a 69-year-old female with a history of depression and hypertension who received OxyContin (10mg twice daily) for intra/post operative analgesia and ondansetron (4 mg twice daily) for antiemetic supportive care following knee replacement procedures. One day later, the patient became agitated, confused, drowsy, was hallucinating, and was diagnosed with serotonin syndrome. The patient slowly recovered within 3-4 days after withdrawal of OxyContin and ondansetron. Concomitant therapy included amiloride, diazepam, orlistat, phenelzine and ramipril.

MAH Comment: Ondansetron therapy, known to be associated with serotonin syndrome, may serve as a plausible alternative explanation. According to the CCDS, OxyContin is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

CAN-2009-0000956 (drug dependence) involved a 44-year-old male with a history of blood lipid fluctuation, DVT, diabetes mellitus and narcotic addiction (codeine, fentanyl, OxyContin and hydromorphone) status post unsuccessful detoxification attempts at a detox centre. Concomitant medications included ranitidine, insulin aspart, insulin glargine, and acetaminophen / codeine phosphate. He was prescribed OxyContin (120mg every 8 hours) for pain relief from pancreatitis and developed leg swelling, infection and inflammation with purple discoloration in the legs, and increased pain. The swelling disappeared following a switch to fentanyl and recurred upon rechallenge with OxyContin.

MAH Comment: Based on the positive dechallenge and rechallenge, the causal role of OxyContin in the occurrence of the leg swelling cannot be excluded. Peripheral edema and drug dependence are listed events in the oxycodone CCDS. The patient's underlying diabetes mellitus, which is associated with an increased risk of infection, and prior history of DVT, which may result in lower extremity venous drainage issues and edema, may have contributed to the patient's events.

GBR-2009-0005611 (drug dependence) involved a 21-year-old male with a history of an addiction to OxyNorm who was started on OxyNorm and experienced cold legs and a lack of feeling in legs. He was subsequently weaned off treatment with OxyNorm and experienced withdrawal symptoms (hypoesthesia and paresthesia). Concomitant medications included tramadol and zolpidem tartrate for unknown indications.

MAH Comment: Based on compatible chronology, a contributory role of oxycodone cannot be excluded. Of note, drug dependence, paresthesia and withdrawal symptoms are all listed events in the oxycodone CCDS.

USA-2009-0038200 (drug addiction) involved a 55-year-old male with a history of spinal fusions and back operations who was started on OxyContin and after an unspecified period of time was hospitalized for drug addiction and had had a "near-death experience" (not further specified). The patient had previously been treated with OxyContin without incident.

MAH Comment: There is insufficient information to assess the causal relationship between oxycodone and the patient's "near death experience." Drug dependence is a listed event in the oxycodone CCDS.

USA-2009-0038561 (intestinal drug misuse) involved a female patient who injected OxyContin and developed an abscess on her spine and became paralyzed. The outcome of the events was not reported.

MAH Comment: Abscesses are a known complication of drug abuse with the injection of opiates.

Renal and Urinary Disorders

GBR-2009-0005204 (renal failure acute) involved a 91-year-old male who was admitted to the hospital due to urinary retention, faecaloma and acute renal failure during treatment with OxyContin. Other drugs included OxyNorm 5mg once daily as needed. On admission the patient was confused and disoriented. Bladder retention and faecaloma were treated with opioid withdrawal, faecaloma evacuation, and an indwelling urinary catheter resulting in full recovery.

MAH Comment: Based on the available information, a contributory role of oxycodone cannot be excluded. Urinary retention, constipation, and ileus are all listed events in the oxycodone CCDS. The acute renal failure was likely secondary to the acute urinary retention precipitated by opioid therapy in an elderly male with probable prostate enlargement.

USA-2009-0039983 (renal failure acute) involved a male patient on pregabalin, celecoxib and ramipril who experienced a fall and was admitted to the hospital where he was given OxyContin. The hospital was unaware that he was also on Lyrica. The patient experienced excessive sedation and was taken to intensive care unit. A drug interaction between pregabalin and oxycodone was suspected. When the patient was allowed to take his celecoxib, he went into acute renal failure. No further details provided.

MAH Comment: The oxycodone CCDS states that there can be enhanced central nervous system depressant effects during concomitant therapy with drugs that affect the CNS. Therefore, an interaction between pregabalin and oxycodone leading to excessive sedation cannot be ruled out. There is insufficient information to assess the causal relationship between oxycodone therapy and the acute renal failure.

Respiratory, Thoracic and Mediastinal Disorders

USA-2009-0037896 (pulmonary edema) was received via the US news media and involved a 23-year-old male with a history of drug and alcohol abuse, motor vehicle accident (MVA), head injury, left leg amputation, an unspecified vena cava surgery and thoracotomy procedure who died due to a reported drug overdose (methadone, OxyContin and marijuana (cannabis). According to the autopsy and toxicology reports the cause of death was pulmonary edema. Toxicology was positive for oxycodone, methadone, THC (detla-9-tetrahydrocannabinol), clonazepam, mirtazapine, and levetiracetam.

MAH Comment: Based on the autopsy and toxicology report the patient expired from pulmonary edema with signs of brain edema. The latter events are likely due to a multiple drug overdose. The current CCDS states that oxycodone "should be used with particular care in patients with a history of alcohol and drug abuse."

USA-2009-003505 (sleep apnea syndrome) refers to a female patient with complex regional pain syndrome (CRPS) taking OxyContin 80 mg three times a day for chronic pain. The physician stated that an independent medical examiner reviewer recommended that the patient be taken off of OxyContin because it was causing sleep apnea and mood disorders, which were exacerbating her underlying depression and hyperalgesia. No further details provided.

MAH Comment: There is insufficient information to confirm the diagnosis of sleep apnea syndrome, nor to assess the causal relationship between the events and oxycodone therapy. Of note, affect liability, depression and respiratory depression are listed events in the oxycodone CCDS.

Skin and Subcutaneous Tissue Disorders

USA-2009-0038170 (angioedema) involved a patient who had been treated with OxyContin and experienced angioedema, tightness in chest, "lips blew up" and "was ripping skin off." The outcome of the events was not reported.

MAH Comment: There was insufficient information to assess the causal relationship between oxycodone and the patient's symptoms. Of note, anaphylactoid, anaphylactic and hypersensitivity reactions are all listed in the oxycodone CCDS.

GBR-2009-0005228 (blister) involved a 78-year-old female with a history of hypertension and sarcoma excision on multiple concomitant medications who experienced blisters 3 days after

initiating OxyContin (10mg twice daily) and 4 days after initiating cefuroxime and metronidazole. OxyContin was discontinued and the patient was recovering.

GBR-2009-0005668 (blister) involved a 41-year-old female who was taking multiple concomitant medications for various indications and was started on OxyNorm 10 mg for pain. On the same day she initiated OxyNorm, the patient developed a red face and blisters, causing her to have a panic attack. OxyNorm was withdrawn, treatment with piriton was given, and the events resolved later the same day.

MAH Comment: Based on the positive temporal association, a causal / contributory relationship between oxycodone therapy and the blisters in the latter 2 cases cannot be ruled out. Of note, hypersensitivity reactions are listed in the oxycodone CCDS.

Surgical and Medical Procedures

GBR-2009-0037327 (hospitalization), reported in a prior PSUR, involved a 70-year-old male who was chewing his medications (including OxyContin) with apple sauce. The follow-up information revealed that the patient had a history of chronic renal failure, chronic lymphocytic leukemia, and metastatic small cell bladder cancer. The patient would get very tired at times and at other times seemed extremely agitated. He was discharged to a skilled nursing facility and OxyContin was eventually discontinued. The patient died one week later. The cause of death was not reported.

MAH Comment: The CCDS states that the controlled release tablets must be swallowed whole, and not broken, chewed, or crushed. The administration of broken, chewed, or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. Agitation and asthenic conditions are listed events in the oxycodone CCDS. Additional information including the patient's concomitant medications, the cause of death and the autopsy report (if available), would be important for a proper medical assessment.

Vascular Disorders

GBR-2009-0005407 (thrombophlebitis) involved a 58-year-old female with a history of mental retardation, breast cancer (status post mastectomy, lymph node dissection and radiotherapy), bone metastases in 2007 (treated initially with letrozole) who experienced thrombophlebitis of the leg while being treated with OxyNorm, OxyContin, cyamemazine, pipamperone, tamoxifen, tramadol, disodic clonronic acid, fluphenazin, mianserin and tropatepin. The patient was treated with enoxaparin and the thrombophlebitis resolved without sequelae.

MAH Comment: There is insufficient information to assess the causal role of oxycodone in the occurrence of the thrombophelbitis. The patient's underlying breast malignancy, which is associated with an increased risk of thrombophlebitis, and tamoxifen therapy, known to be associated with the occurrence of DVT, may serve as plausible alternative explanations for the patient's event.

Non-serious Cases

Of the 432 reports, 51 were determined to be non-serious. Thirty cases involved a primary AE term that appeared only once; a list of these reports by MedDRA® SOC and PT appears below in Table V.

Table V
Non-serious Cases Involving a Primary AE Term that Appears Only Once, by SOC
(N = 30)

SOC	PT
Cardiac disorders	Palpitations
Eye Disorders	Lacrimation increased
Gastrointestinal disorders	Rectal discharge
General disorders and administration site conditions	Condition aggravated Drug withdrawal syndrome Energy increased General physical heath deterioration Pain Pyrexia Sense of oppression Therapy naïve
Infections and infestations	Tooth infection
Injury, poisoning and procedural complications	Head injury Unwanted awareness during anaesthesia
Investigations	Blood pressure increased Weight increased
Metabolism and nutrition disorders	Hypoglycaemia Hypophagia
Musculoskeletal and connective tissue disorders	Back pain Joint swelling
Psychiatric disorders	Delirium Dysphoria Nightmare
Renal and urinary disorders	Renal impairment Urine odour abnormal
Reproductive system and breast disorders	Gynaecomastia
Respiratory, thoracic and mediastinal disorders	Asthma Respiratory disorder
Skin and subcutaneous tissue disorders	Skin discoloration
Vascular disorders	Flushing

Of the 51 non-serious cases, 21 cases included primary AE terms that appeared more than once. These events include: medication residue (n=9); drug effect increased (n=5); drug intolerance (n=4); and, migraine (n=3). These terms may be considered expected, even if not explicitly listed in the oxycodone CCDS. None suggest any significant new risk attributable to oxycodone. These non-serious adverse event terms reported during this PSUR period are generally consistent with the medical concepts presented in the CCDS.

7. STUDIES

This section contains a summary of all newly analyzed studies (section 7.1) from clinical (section 7.1.1) and non-clinical (section 7.1.2) sources.

This section also contains a general overview of all studies planned, initiated or continuing during the reporting period (section 7.2) from clinical (section 7.2.1) and non-clinical (section 7.2.2) sources. Though none are specifically investigating a safety issue as primary endpoint, all of these studies collect data on safety as part of the standard data collection practice.

There were no safety findings reported with a potential impact on product safety or the CCDS in any of these studies. A summary of these studies with any relevant safety reports is presented below.

7.1 Newly Analyzed Company-Sponsored Studies

Three (3) company-sponsored clinical studies were completed and newly analyzed during the report interval of 13 April 2009 through 12 October 2009; two (2) in China and one (1) in Slovakia.

There were no company sponsored non-clinical studies newly analyzed during the reporting interval of 13 April 2009 through 12 October 2009.

7.1.1 Clinical Studies

During the reporting interval of 13 April 2009 through 12 October 2009 three (3) studies were completed and analyzed.

- **China**

Two (2) studies were completed and analyzed in China. A summary of the final study reports are presented below

1) **Study Title: (OXY-CN-07-040) Open labeled, self controlled, multi-center PMS studies of OxyContin® Tablets for moderate to severe chronic muscular skeletal pain and arthralgis**

Study Dates: From April 2007 to June 2008

Study Status: Completed.

Phase of Development: Post Marketing observational study

Objectives: Clinical observation of the efficacy and safety on OxyContin® Tablets 5mg, 10mg, 20mg & 40mg in patients of moderate to severe chronic muscular skeletal pain and arthralgia, in order to provide more experience to Chinese hospitals and doctors.

Methodology: This study is a multi-center, open label, self-controlled post marketing surveillance. The observation period is 2 weeks.

Number of Subjects: 166

Indication and Criteria for Inclusion:

Enrollment Criteria:

1. Patients diagnosed as muscular skeletal pain or arthralgia by medical doctors (exclude cancer pain) and inadequate analgesia efficacy in preliminary with NSAIDs or opioid analgesic or insufficient tolerability of both groups of substances.
2. Age between 40-70 years old, body weight >= 40kg, with more than 4 weeks pain history (except for patients with AIDs or paraplegia) as guided by China State Food and Drug Administration, P.R.China (SFDA)
3. Without opioid abuse history
4. Able to communicate with doctors and able to visit hospitals easily and sign patient consent form

Exclusion Criteria:

1. Pregnant or lactating women.
2. Having history of opioid drug abuse.
3. Patients with a history of the following conditions: hypo-oxygenic respiratory suppression; head injury; paralytic ileus; acute abdominal syndrome; stomach empty delay; chronic obstructive pulmonary disease; cor pulmonale; chronic bronchial asthma; high carbonic acidemia; moderate to severe liver dysfunction; severe renal insufficiency (creatinine clearance rate<10ml/min; severe constipation; concomitant use of Mono-Amine Oxydase Inhibitors (MAOI); Within two weeks after discontinuation of MAOI.
4. Patients who have contraindication mentioned in Oxycontin® Package Insert which, in the opinion of the investigator, exposes the patient to risk by participating in the study.
5. Allergy to Oxycodone hydrochloride or other ingredients in the OxyContin® tablets.

Test Treatment, Dose, and Mode of Administration:

Qualified patients receive Oxycontin treatment twice daily for up to 2 weeks.
For patients with pain score assessed at 5-6 point, initial dose is 5mg/12h.
For patients with pain score assessed at 7-10 point, initial dose is 10mg/12h.
For opioids naive patients, starting dose is recommended as 5mg/12h.
Dose conversions should be made for those patients already receiving opioids.
Dose titration will conducted afterwards following information on product leaflet.
Doctor can prescribe anti-emetic drug and laxatives before or during patient taking OxyContin.
Immediate release opioid analgesic can be used when breakthrough pain occurs.
During the treatment by Oxycontin, drugs with direct analgesic effect should be avoided. Patients receiving a NSAID at enrollment shall continue at the same dose throughout the trial.

Duration of Treatment: 2 weeks

Results:

General information: Number of subjects for per protocol set was 166, with 70 male subjects (47.30%) and 78 female subjects (52.70%), and mean age was 56.69±8.25 years old; 82.88% subjects were outpatients. 27.03% patients had osteoarthritis, followed by lumbar disc herniation (23.65%), low back pain (20.95%), spinal stenosis (18.24%), osteoporosis (13.51%), backache (10.14%) etc.. The most sites of the pain occurred were at back / spine (90 cases, 60.81%), followed by knee / elbow joint (44 cases, 29.73%), shoulder / hip joint (38 cases, 25.68%), left thigh / leg / foot (18 cases, 12.16%). Mean course of disease was 17.44±25.94 months (1~240 months).
Treatment: Mean daily dose was 17.19±6.90 mg for the 148 patients (10.00mg~41.43mg, median was 20.00). Mean daily dose was below 30mg for 95.27% patients.
Onset of action for the first dose: Onset of action was within 30 minutes for 27.03% patients, within 30~45 minutes for 43.24% patients, and within 45~60 minutes for 22.97% patients, i.e. onset of action for the first dose was within 1 hour for 93.24% patients. Duration of pain relief was up to 12 hours for over 83.67% patients.
Efficacy analysis: Prior to treatment, the mean pain score was 6.52±1.38 for the 148 patients with chronic skeleton, muscle and joint pain, however the score was decreased to 2.24±1.54 at the end of 1 week treatment and was 1.42±1.14 at the end of 2 weeks treatment, and the difference comparing with that of baseline was statistically significant (P<0.0001). Total effective rate was 97.97% after 1 week of treatment; and was over 99.29% at the end of 2 weeks treatment. Sleep quality was significantly improved.
Safety: Incidence of adverse drug reaction was low. Incidence of adverse drug reaction was 27.11% at the end of 1 week treatment, and was 5.20% at the end of 2 weeks treatment. The most common adverse drug reaction was nausea; and common adverse drug reactions were: vomiting, constipation, dizziness, headache, drowsiness, itch of skin; uncommon adverse drug reaction was: asthenia. A trend was shown that the type and the incident of adverse drug reactions mentioned in the study were reduced gradually with the duration of treatment. Using drugs could prevent adverse reaction occurrence and decrease the incidence of adverse reaction. No adverse drug reactions such as respiratory depression, dysuria, hallucinations were noted. No withdrawal syndromes with physical dependence occurred after drug administration stopped. No psychological dependence occurred.
Conclusion:
Oxycontin® can provide good management of moderate to severe chronic skeleton, muscle and joint pain in a quick and effective manner, with satisfactory analgesic efficacy and safety.

This is a non-interventional trial.

Publication: NA

2) OXY-CN-08-030 - Open labeled, Multi-center, Post-marketing Surveillance for Relieving Moderate to Severe Chronic Cancer Pain

Study Dates: April 2008 – Feb 2009
Study Status: Completed
Phase of Development: Post Marketing observational study

Study Objectives:

- To observe the efficacy and safety of Oxycontin® Tablet during the post marketing use in moderate to severe chronic cancer pain.
- To observe the impact of Oxycontin® to quality of life in patients with moderate to severe cancer pain

Study Method:

This study is a multi-center, open label, self-controlled post marketing surveillance. The observation period is from 2 to 4 weeks.

Number of Subjects:

A total of 1975 cancer pain patients participated in the study. Of them 8 cancer pain patients were excluded from the study due to combined administration with other long-acting opiates drugs influencing efficacy and safety on OxyContin. Therefore, safety set is in 1967 cases, standing for 99.59% of total cases. Because of the protocol violation of 1 case (baseline NRS: 3), full analysis set is in 1966 cases, standing for 99.54% of total cases. Because 5 cases were dropped out during test, per-protocol set is in 1961 cases, standing for 99.29% of total cases.

Inclusion Criteria:

Patients with confirmed diagnosis of moderate to severe cancer pain (VAS score≥4).
Aged over 18 years.
To be able to communicate with physicians and sign the informed consent forms.

Test Treatment, Dose, and Mode of Administration:

Only qualified patients received OxyContin tablets treatment Q 12 hours. For patients with VAS pain scores between 4-6, the initial dosage was 5 mg/12 hours; For patients with VAS pain scores between 7-10, the initial dosage was 10 mg/ 12 hours. If the patients had been on other analgesics and showed a poor tolerability, she/he could be switched to OxyContin tablets according to a dosage-conversion table.

For patient whose initial dosage was 5 mg, the treatment dosage could be increased to 10 mg directly. For patient whose initial dosage was 10 mg or higher, the treatment dosage could be increased by 25% to 50% of the current dosage at each increase.

According to the WHO three-ladder principal for pain management, some medications should be prescribed to prevent side effects, such as Cephaeline Hydrochloride, Senna Leaf to prevent the side effects.

Clinical Evaluation:

Efficacy parameter: pain intensity, response rate, Quality Of Life.
Safety parameter: adverse events, side effects

Statistical Methods:

Efficacy evaluation was analyzed by full analysis set (FAS) and Per-protocol sets (PP) and safety evaluation was analyzed with safety set (SS). SAS9.13 statistical software was used for statistical analysis. Two-tailed test were used for all the statistical tests. Statistical significance was set at P value≤ 0.05.

Result:

General materials: Full analysis population included 1966 patients, of which 1225 patients were male (62.31%) and 741 patients were female (37.69%). The average age was 58.47±11.53 years old. Most subjects (73.22%) were hospitalized patients. Cancer subtypes of the patients included lung cancer (45.97%), abdominal cancer (35.20%), gynecological cancer (4.95%), breast cancer (4.64%), urea-genital cancer (3.62%). 34.12% of the patients presented somatic pain, 31.41% for visceral pain, 21.32% for mixed pain (have at least two type pains of somatic pain, visceral pain, or neuropathic pain), 11.87% for nerve pain due to local invasion or compression. OXYCONTIN was chosen as the first treatment of choice in 1126 patients (57.28%). OXYCONTIN was switched from other second or third ladder analgesics in 840 patients (42.90%).

Medication: Average daily dose of 1967 patients is 37.88±39.46 mg (5mg ~ 617.17mg). The average daily dose was 30mg or lower in 54.34% of patients and was 40 mg or lower in 75.64% of observed patients.

Efficacy analysis: For the efficacy evaluation of anti-pain of total patients' each visiting, as to the full analysis set, the treatment response rate was 82.81% after one week treatment, and 92.73% after two week treatment, 95.17% after three week treatment, up to 97.25% at the end of for weeks. As to the per-protocol set, the treatment response rate was 82.92% after one week treatment, and 92.86% at the end of two weeks. Patients' Quality Of Life was improved significantly.

Safety analysis: The incidence of total adverse event rate was 36.91%, mild, 22.78%, moderate, 15.86%, severe, 0.56%. The most common adverse event was constipation, standing for 25.06%, nausea 11.24%, vomiting 7.27%. Other common adverse event was dizziness 2.39%, dysuria 1.37%, hypersomnia 1.37%. The less common adverse reaction include fatigue 0.97%, illusion 0.25%, headache 0.2%, respiratory depression 0.05%, itching 0.15%.

Conclusion:

OXYCONTIN can relieve moderate and severe cancer pains rapidly and effectively. It has demonstrated a good analgesic efficacy and safety profile.

This is a non-interventional trial

- **Slovakia**

One (1) study was completed in Slovakia. A summary is presented below and the final study report (FSR) is included in Appendix VIII.

OXY-PMS-SK.001 - Post Marketing Surveillance on the efficacy and safety of OxyContin® in the treatment of pain due to degenerative skeletal disorders not responding to pre-treatment with weak opioids with or without NSAR- combination

Name of Finished Product: OxyContin® slow release tablets

Investigator(s)/Centre(s): 88 out-patient departments

Study Initiation: April 2006

Phase of Development: non-interventional study (PMS)

Objectives: Observation of efficacy, safety and well-being in patients suffering from moderate to severe pain due to degenerative skeletal disorders not responding to pre-treatment with weak opioids with or without NSAID-combination or transdermal strong opioids.

Study Design (Methodology): open, non-comparative, non-interventional (PMS). The NIS was carried out according to the requirements of the national drug law.

Number of Subjects: planned approx. 200 patients, completed 315 out-patients

Indication and Criteria for Inclusion/Exclusion:
Male and female patients (> 18 years) with moderate to severe pain due to degenerative skeletal disorders, e.g. osteoarthritis, spondylarthritis incl. low back pain, vertebral disc disorders, osteoporosis, not responding to pre-treatment with weak opioids (+/- NSAR) and posology (inclusion and exclusion criteria) according to OxyContin® SmPC

Test Treatment, Dose, and Mode of Administration: according to SmPC.

Concomitant Medication Including Rescue: Combinations with any commercially available analgesic and co-analgesic medication as well as combinations with any additional concomitant medications which are indicated and commercially available in adherence to SmPC.

Duration of Treatment and Study Duration: 3 weeks (April 2006 to March 2007)

Treatment Schedule (Procedure): Initial daily dose 20 mg OxyContin® (10 mg bid), individual dose titration based on the individual needs for analgesic effect and tolerability. In general OxyContin® was prescribed by the physicians as recommended by the SmPC.

Criteria for Evaluation:

Analysis Populations:

- Enrolled population to include all subjects enrolled in the study
- Full population to include all subjects providing at least one efficacy measurement post treatment
- Safety population to include all subjects providing at least one safety measurement post treatment

Efficacy Assessment(s):

Primary objective:

- Decrease of pain intensity by OxyContin® (analgesic efficacy) by a Visual Analogue Scale (VAS, 0 = no pain, 10 = most intense pain)

Secondary objectives:

- Changes in quality of life, measured by VAS
- Comparison to the pre-treatment
- Drug utilization (frequency and dose application, concomitant treatment)
- Global evaluation of efficacy and safety by physicians and patients.

Interim Analyses: not planned

Safety Assessments:
Safety was assessed by documentation of:

- vital signs,
- self-reported spontaneous adverse drug reactions and
- adverse events.

Standard forms were used for AE and SAE collection/documentation; expedited reporting of SAEs according to the national requirements. All SAEs occurred in this NIS were forwarded to Drug Safety of Mundipharma Research GmbH & Co. KG.

Statistical Methods:

Efficacy Analyses:
All data recorded were entered into a database for descriptive analysis providing tables incl. summary statistics as well as listings of all variables.

Safety Analyses: Descriptive analysis, summary tables for AEs using MedDRA codes.

Comments: This non-interventional study was finalized in July 2008; Final Study Report dated August 25, 2009.

7.1.2 Non-clinical Studies

Purdue Pharma L.P. (PPLP) and affiliated companies did not complete any nonclinical studies with oxycodone hydrochloride during the reporting period 13 April 2009 through 12 October 2009.

7.2 Targeted New Safety Studies Planned, Initiated or Continuing During the Reporting Period

This section contains clinical studies (section 7.2.1) and non-clinical studies (section 7.2.2) that are conducted to obtain data – among others – on safety parameters. These studies do not

investigate a specific safety issue; however, they have been included in this section because relevant safety data is being collected.

Studies listed in this section are planned, initiated or continuing during this reporting period. "Continuing" studies include those studies that are ongoing or have been completed / terminated but for which the Final Study Reports (FSR) are pending.

Results from interim analysis are contained in this section.

7.2.1 Clinical Studies

There were a total of fourteen (14) planned, initiated, or continuing clinical studies during the reporting interval of 13 April 2009 through 12 October 2009.

- **China**

One (1) study was completed in China during the reporting interval of 13 April 2009 through 12 October 2009 for which data analysis is ongoing.

1) **OXY-CN-08-060 - Post Marketing Surveillance of OxyContin for Diabetic Peripheral Neuropathy (DPN) Pain in China**

   a) **Start date:** from April-2008
   b) **Planned number of patients**: 80 patients
   c) **Present status:** Patient enrollment and data collection is completed. A total of 84 completed Case Report Forms has been collected and data analysis is on-going. No important safety information found so far for this study.
   d) **Phase of Development:** Post -Marketing observational study
   e) **Objectives:**
      1. To observe the efficacy and safety of Oxycontin® Tablets during the post marketing use in patients with moderate to severe chronic pain of DPN;
      2. To observe time to pain relief onset, the lasting time of pain relief and time to reach stable state of titration for patients using Oxycontin® Tablet ;
      3. To observe the impact to quality of life of Oxycontin® in patients with moderate to severe pain caused by DPN.
   f) **Methodology:** This is a multi-center, open label study. The maximum study treatment will be 6 weeks
   g) **This is a non-interventional trial.**
   h) **Publication:** NA

- **Czech Republic**

One (1) non-interventional study was started in the Czech Republic during the reporting interval of 13 April 2009 through 12 October 2009.

OXY.NIS.CZ.003 – OxyContin in the Treatment of Chronic Pain

Name of Finished Product: OxyContin® prolonged-release tablets	**Name of Active Ingredient:** Oxycodone hydrochloride	
Protocol No.: OXY.NIS.CZ.003	**Temporary (T) No.:**	**<EUDRACT><IND> No.:** Not applicable
Short Title of the Study: OxyContin® in the treatment of chronic pain		
Full Title of the Study: OxyContin in the treatment of chronic cancer and non-cancer pain		
Investigator(s)/Centre(s): 80		
Study Initiation: September 2009	**Phase of Development:** Non-interventional study (NIS)	
Objectives: Observation of efficacy, safety and well-being in patients suffering from chronic cancer or non-cancer pain either newly treated or switched from pre-treatment with weak opioids with or without NSAID-combination [WHO II] or strong opioids due to insufficient pain control		
Study Design (Methodology): Open, non-comparative, non-interventional (Post Marketing Surveillance). The NIS will be carried out in accordance with the national drug law.		
Study Design Graphic: not applicable		
Number of Subjects: 400 patients		
Indication and Criteria for Inclusion/Exclusion: Male and female patients (> 18 years) with chronic severe cancer or non-cancer pain not responding to pre-treatment with weak opioids (+/- NSAID) or other strong opioids. Posology, inclusion and exclusion criteria, contraindications and precautions according to Oxycontin SmPC.		
Test Treatment, Dose, and Mode of Administration: Oral treatment with OxyContin® 10 mg, 20 mg, 40 mg or 80 mg. In general, OxyContin® is administered at an initial dose of 20 mg (= 10 mg bid) according to dose of pre-treatment, actual pain intensity and constitution. Further titration and maintenance of the daily dose and the time of the day for intake were based on the individual needs for analgesic effect and tolerability. Due to the non-interventional character of the study, OxyContin® is prescribed by the decision of the individual physician. In general, OxyContin® is utilized as recommended by the SmPC.		
Reference Treatment, Dose, and Mode of Administration: not applicable		
Concomitant Medication Including Rescue: Combinations with any commercially available analgesic and co-analgesic medication as well as combinations with any additional concomitant medications which are indicated and commercially available in adherence to SPC.		
Duration of Treatment and Study Duration: 4 weeks		

Treatment Schedule (Procedure): Initial daily dose: 20 mg OxyContin® (= 10 mg bid), individual dose titration based on the individual needs for analgesic effect and tolerability. In general, OxyContin® is utilized by the physicians as recommended by the SmPC.
Criteria for Evaluation:
Analysis Populations: Full analysis of all included patients for safety and efficacy
Efficacy Assessment(s): Primary objective: • Decrease of pain intensity by OxyContin® (analgesic efficacy) by a Visual Analog Scale (0 cm= no pain, 10 cm = most intense pain) Secondary objectives: • Changes in quality of life, measured by VAS (quality of life parameters activity, sleep quality and mood) by patient self evaluation (modified according to pain questionnaire Pain Research Group, Wisconsin-Madison Medical School). • Comparison to pre-treatment. • Drug utilization (frequency and dose application, concomitant treatment) • Global evaluation of efficacy and safety by physicians and patients
Drug Concentration Measurements: not applicable
Bioanalytical Methods: not applicable
Pharmacodynamic Measurements: not applicable
Safety Assessments: Safety will be assessed by evaluation of spontaneously reported and documented adverse events. Standard forms will be used for AE and SAE collection/documentation; expedited reporting of SAEs occurs according to the national requirements. All SAEs occurring in this NIS will be forwarded to Drug Safety of Mundipharma Research GmbH & Co. KG.
Statistical Methods:
Efficacy Analyses: descriptive analysis, comparisons for decrease of pain intensity and for changes in quality of life (day 0 vs. day 14, day 28)
Interim Analyses: not applicable
Pharmacokinetic and/or Pharmacodynamic Analyses: not applicable
Safety Analyses: descriptive analysis, frequency and observed pattern of adverse events, intensity of AEs, observed unexpected adverse events, or signals which might be detected by the NIS
Sample Size Rationale: not applicable

- **France**

Two (2) studies were ongoing in France during the report interval of 13 April 2009 thru 12 October 2009.

1) OCS 2 - National French therapeutic survey in chronic cancer pain patients treated with OxyContin®LP

Name of Finished Product: OxyContin®LP
Study Objectives: • Main objective: To identify pain profiles in chronic cancer pain patients treated with OxyContin®LP • Secondary objectives: -profiles of patients treated with OxyContin®LP -pain characteristics -breakthrough pain characteristics
Study Duration: 1 January 2009 – 31 July 2009 **Study Status:** on going **Phase of Development:** Post Marketing observational survey
Study Method: This is an observational, transversal, multi-center, open label, post marketing survey
Number of Subjects: A total of 277 out patients and hospitalized chronic cancer pain patients are planned in the study. They were recruited by 52 pain or palliative care specialists in hospital.
Inclusion Criteria: Chronic Cancer Pain Patients treated with OxyContin®LP. Out patients or hospital patients but not in pain or palliative structure Aged over 18 years. Able to communicate with physicians and sign the informed consent forms. Well completed patient's file
Test Treatment, Dose, and Mode of Administration: Observational survey in real condition of prescription and use of OxyContin®LP in patients who received OxyContin®LP tablets
Clinical Evaluation: Pain treatment management, compliance Safety parameter: adverse events, side effects (Bowel Function Index)
Statistical Analysis: Qualitative items will be described with usual statistic tools: sample, percentage Quantitative items will be described with median, mean, standard deviation
Result: Not available
Conclusion: Results in 2010 **This is a non-interventional trial**

Name of Finished Product: OxyContin® LP

2) EPOXY - compliance survey in pain patients treated with OxyContin®LP measured with the Smart Blister® in real condition of life with retail pharmacists

Name of Finished Product: OxyContin®LP
Study Objectives: • Main objective: objective compliance of measure of OxyContin®LP treatment in pain patients • Secondary objectives: -retail pharmacists delivery practices -description of pain cancer out-patient management in usual practice
Study Duration: October 2008 – 31 December 2009 **Study Status:** on going **Phase of Development:** Post Marketing observational survey
Study Method: This is an observational, prospective, multi-center, open label, post marketing survey
Number of Subjects: A total of 200 out-patients treated for pain are planned in the survey. They are recruited by 100 retail pharmacists; 82 patients are recruited in October 2009
Inclusion Criteria: Pain Patients treated with OxyContin®LP. With Smart Blister®
Test Treatment, Dose, and Mode of Administration: Observational survey in real condition of delivery and use of OxyContin®LP in patients received OxyContin®LP tablets: survey organized with retail pharmacists
Clinical Evaluation: Pain treatment management, compliance Safety parameter: adverse events
Statistical Analysis: Qualitative items will be described with usual statistic tools: sample, percentage Quantitative items will be described with median, mean, standard deviation
Result: Not available

Conclusion: Results in 2010 **This is a non-interventional trial**
Name of Finished Product: OxyContin® LP

- **Japan**

Two (2) clinical studies (0809V9131 & 0811V9133) and three (3) PMS studies (V1270, V1271, and V9132) were ongoing in Japan during the reporting interval of 13 April 2009 – 12 October 2009.

1) **0809V9131 - An open labeled, multi-center study to assess the efficacy, safety and tolerability of continuous intravenous oxycodone injection (S-811717) for the treatment of cancer pain.**

   a) **Start date:** from December 2008

   b) **Planned number of patients**: 70 patients

   c) **Present status:** The patient enrollment is on-going. So far there are 49 patients enrolled. The study will be closed by the beginning of 2010. No important safety information found so far in this study.

   d) **Phase of Development:** Phase 3

   e) **Objectives:**
      - To observe the efficacy and safety of the intravenous oxycodone injection for moderate to severe chronic cancer pain.
      - To evaluate the pharmacokinetics of oxycodone after an oxycodone hydrochloride injection (intravenously as a single bolus dose or by continuous administration).

   f) **Methodology:** This is a multi-center, open labeled, dose titration study.

   g) **This is a confirmatory trial.**

   h) **Publication:** NA

2) **0811V9133 - An extension study of the 0809V9131 study to assess the safety and tolerability of continuous intravenous oxycodone injection (S-811717) for the treatment of cancer pain.**

   a) **Start date:** December-2008

b) **Planned number of patients**: Not designed

c) **Present status:** The patient enrollment is on-going. So far there is 9 patient enrolled. The clinical study 0811V9133 will be closed by the date of approval for the manufacture and sale regarding S-0811717. No important safety information found so far in this study.

d) **Phase of Development:** Phase 3

e) **Objectives:**
1) To observe the safety of the intravenous oxycodone for moderate to severe chronic cancer pain.

f) **Methodology:** This is a multi-center, open labeled, dose titration study.

g) **This is a confirmatory trial**.

h) **Publication:** NA

3) V1270 - Investigation on the rescue medication of OxyNorm® Powder 0.5%

a) **Objective:** Investigation of the safety and efficacy of the use of immediate-release oxycodone hydrochloride preparation OxyNorm® Powder 0.5% as rescue medication at the regular administration times of sustained-release oxycodone hydrochloride preparation (OxyContin® Tablets).

b) **Starting Date:** March 2007

c) **Projected Completion:** 31 May 2009

d) **Study Participants:** Hospital in patients given OxyNorm® Powder 0.5% as rescue medication at the regular administration times of OxyContin® Tablets.
300 Patients.

e) **Methodology:** Observational, non-interventional, post-marketing surveillance study

f) **Number of Subjects:** 319 patients enrolled, 303 completed

g) **Safety Summary:** There is no interim analysis information available at this time.

4) V1271 - Investigation on the dose adjustment using OxyNorm® Powder 0.5% and the switch-over to OxyContin® Tablets

a) **Objective:** Investigation of the safety and efficacy of using OxyNorm® Powder 0.5% to

determine the initial optimal dose and also the safety and efficacy after switching over to OxyContin® Tablets.

b) **Starting Date:** March 2007

c) **Projected Completion:** 31 August 2009

d) **Study Participants:** Patients given OxyNorm® Powder 0.5% as regular administration for the purpose of determining the initial optimal dose.
50 Patients

e) **Methodology:** Observational, non-interventional, post-marketing surveillance study.

f) **Number of Subjects:** 56 patients enrolled, 46 completed

g) **Safety Summary:** There is no interim analysis information available at this time.

5) V9132 - An open labeled, multi-center study to assess the efficacy, safety and tolerability of continuous subcutaneous oxycodone injection (S-811717) in patients with cancer pain.

Study Dates	1 June 2009 – 31 Jan 2010
Study Status	The patient enrollment is on-going. So far there are 9 patients enrolled.
Objectives	•To evaluate the pharmacokinetics of oxycodone after continuous subcutaneous administration. •To observe the efficacy and safety of subcutaneous administration of oxycodone in patients with moderate to severe chronic cancer pain.
Methodology (Design)	This study is an open labeled, multi-center, confirmatory trial.
Test Drug(s)	oxycodone hydrochloride
Dose Regimen, Route of Administration, Formulation(s)	Dose Regimen; The dose can be individually titrated to an effective dose that provides adequate analgesia and minimizes undesirable effects Route of Administration/Formulation; subcutaneous injection
Comparator Drug(s)	none
Dose Regimen, Route of Administration, Formulation(s)	-

Treatment Duration	The observation period is 7days.
Total No. of Subjects	20 patients
Safety Findings (incl. No. of Patients)	SAE has been reported in 1patient until now. (PT term: neoplasm malignant, Outcome: fatal, Causality: not related)
Comment	

- **Korea**

One (1) study was planned in Korea during the report interval of 13 April 2009 – 12 October 2009.

OPD08-KR-001 - Observational Study for Oral Controlled Release Strong (Narcotic) Opioid for Cancer Pain Management in Korean Cancer Patients

Objectives	This study is to evaluate the safety and efficacy of oral controlled-release strong opioid products in patients with moderate to severe cancer-related pain
Methodology (Design)	Non-interventional prospective observational study
Start Date:	Q1 2009
Test Drug(s)	Oral opioid drug in controlled-release formulation marketed in Korea (including OxyContin)
Dose Regimen, Route of Administration, Formulation(s)	Not applicable
Comparator Drug(s)	None
Dose Regimen, Route of Administration, Formulation(s)	None
Treatment Duration	Observational period up to 8 weeks
Total No. of Subjects	Approximately 400 patients
Safety Findings (incl. No. of Patients)	In case of any SAE, study personnel report to corresponding manufacturers and regulatory affair accordance with local regulation.

Comment	This non-interventional, observational study will be conducted as a collaborative effort with Korean Society of Hospice and Palliative Care.

- **Philippines**

One (1) study was ongoing in the Philippines during the report interval of 13 April 2009 – 12 October 2009 and one (1) study suspended as of November 2007, is expected to resume by Q2 of 2010.

1) Monitored Release (Post-Marketing Surveillance) Study on OxyNorm

a) **Design:** Open, non-comparative, multi-center study

b) **Objectives:** Measure of efficacy and safety of OxyNorm® as used in clinical practice for moderate to severe pain. Measure of efficacy is pain relief response; measure of safety is presence or absence of adverse events.

c) **Investigators:** Multi-center, nationwide. Recruitment of investigators started in April 2007.

d) **Treatment:** As per usual clinical use of opioid analgesic in terms of equivalents of morphine (immediate release); maximum of 14 days treatment under observation with dose titration according to response to treatment. OxyNorm® used as primary treatment for pain or as rescue medication for other opioids, e.g., OxyContin®.

e) **Number of evaluable cases to complete study:** 500

a. Number of subjects enrolled at the time of the data lock for this PSUR: 1,169
b. Number of subjects initially projected for involvement: 700
c. Number of randomized subjects: 0
d. Number of subjects who completed the study: 1,546

f) **Start date:** 2Q 2008

g) **Duration:** 1 year. Scheduled to end in 2Q 2009.

h) **Population:** Males or females 18 years or older with moderate to severe pain by VAS score.

i) **Comments:** Oxycodone is being studied currently using the OxyNorm® post-marketing surveillance study known in the Philippines as Monitored Release Study and performed on orders of the local health authority (BFAD). The study is ongoing and there has not been any report of serious adverse event. All other adverse events reported will be compiled in the report at the end of the study.

j) **This is a non-interventional study**

2) Monitored Release (Post-Marketing Surveillance) Study on OxyContin®.

a) **Description:** This is a study mandated by the local Regulatory Authorities (also known as BFAD - Bureau of Food and Drug). The regulatory agency has exercised its option to require the company to perform an observational study on the safety and efficacy of OxyContin® products as used in clinical practice.

b) **Design:** Open, non-comparative, observational study

c) **Objectives:** Monitor the Safety (adverse events) and efficacy (pain control) of OxyContin when used in routine clinical practice

d) **Start date:** 2Q 2009

e) **Duration:** Scheduled to end in 4Q 2009.

f) **Present status:** The study was suspended in 2007 to give way to the requirements of BFAD (currently FDA). The Study was resumed in 2008. Received 454 case report forms to date. Protocol was under revision on order of the Regulatory Authorities (BFAD) so that OxyContin® 5 mg may be included in the study. Original protocol included only OxyContin® 10, 20, 40 and 80 mg. The reason for suspension was a BFAD order to stop the study so that another dosage form (OxyContin® 5 mg) could be included. This is administrative on the part of BFAD. There was no safety issues involved.

g) **Target Date of Resumption:** Hope to resume by Q2, 2010. There is an approved protocol but this has not started yet due to administrative reasons.

h) **Number of evaluable cases to complete the study:** 700 evaluable cases.

a. **Number of subjects enrolled at the time of the data lock for this PSUR:** 0
b. **Number of subjects initially projected for involvement:** 700
c. **Number of randomized subjects:** 0
d. **Number of subjects who completed the study:** 454

i) **Safety Summary:** No interim report available.

j) **This is a non-interventional study**

- **Switzerland**

There was one (1) ongoing study in Switzerland for which there were no additional subjects and safety findings during the reporting interval of 13 April 2009 – 12 October 2009

Ethics Committee Number: 202/06
Determining optimal drug regimen in individual patients with chronic pain

Objectives	Development and application of a new optimization model to find the optimal combination of different analgesic combinations in individual patients with chronic neuropathic and chronic musculoskeletal pain
Methodology (Design)	The method "mathematic model" was already used (Curatolo M, Schnider T, Petersen-Felix S, Weiss S, Signer C, Scaramozzino P, Zbinden A: A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl, and clonidine for postoperative analgesia. Anesthesiology 2000; 92: 325-37) and is described (Berenbaum MC: Direct search methods in the optimization of cancer chemotherapy regimens. Br J Cancer 1990; 61: 101-9). Patients will have to complete at least 4 daily pain diaries during the 7 days prior to randomization, using a visual analogue scale with 0 as non pain and 10 as worst possible pain, with an average score ≥3 out of 10 over this period being an inclusion criteria to participate in the study.
Test Drug(s)	Combinations of Amitriptyline (Tryptizol), Pregabalin (Lyrica), Oxycodone (OxyContin®)
Dose Regimen, Route of Administration, Formulation(s)	Patients will have to complete at least 4 daily pain diaries during the 7 days prior to randomization, using a visual analogue scale with 0 as non pain and 10 as worst possible pain, with an average score ≥3 out of 10 over this period being an inclusion criteria to participate in the study. Each oral combination will be given during 1 week without a washout period. The initial complex will include 4 orally combinations at choice of the investigator, that are expected to produce analgesia with no or minimal side effects. Thus the initial set of combinations will be studied during a period of 4 weeks. Patient will get a set of standard dose capsules to take every 12 hours during the week. Patients, physician in charge, staff who informed patients and collected the data will not be aware of the dosage of the drugs used at the particular optimization step. The hospital pharmacy will take care of the correct dose and blinding, using neutral looking capsules containing the investigated regimen defined by blinded investigators for each optimization step. Pregabalin: 50-600mg/d Oxycodone: 10 mg/d, no maximum value

	Amitriptyline 10-100 mg/d
Comparator Drug(s)	-
Dose Regimen, Route of Administration, Formulation(s)	-
Treatment Duration	Each oral combination will be given during 1 week without a washout period. Study duration: 2 years
Total No. of Subjects	15
Safety Findings (incl. No. of Patients)	-
Comment	-

- **United Kingdom**

One (1) clinical study was ongoing in the UK during the reporting interval of 13 April 2009 – 12 October 2009.

OXI3001 - An open, multi centre, non-comparative observational study to assess the safety and tolerability of Oxycodone hydrochloride injection 50 mg/mL as a subcutaneous infusion in subjects with severe cancer pain. An open, multi-centre, single therapy, non-comparative study, using Oxycodone hydrochloride injection 50 mg/mL delivered as a subcutaneous infusion to subjects with severe cancer pain, for up to 20 days duration

Number of Subjects: Up to 50 subjects recruited over a 9 month period.

Indication and Criteria for Inclusion/Exclusion:
Inclusion Criteria

1. Male or female subjects aged 18 years and above, who have severe cancer pain.
2. Subjects who require a strong opioid by subcutaneous infusion to stabilize and manage their cancer pain effectively.
3. Subjects who give written informed consent to participate in the study.
4. Subjects who agree to their primary care physician being informed of their participation in the study.
5. Subjects who consent to processing of their trial data according to the requirements of the UK Data Protection Act 1998.

Exclusion Criteria

1. Subjects who are pregnant, lactating or in the Investigators opinion are at risk of conceiving and are not using adequate contraception measures.
2. Subjects with known hypersensitivity (allergic reaction) to oxycodone, any other opioids or any of the excipients.
3. Subjects who are planned to receive chemotherapy during the study treatment period or are currently receiving continuous I.V. chemotherapy infusion.
4. Subjects with neutropenia, thrombocytopenia or coagulation disorders.
5. Subjects with any contraindications to oxycodone as outlined in the Investigator Brochure or Summary Product Information sheet for oxycodone.
6. Subjects who are currently participating in another clinical research study involving a new chemical entity.
7. Subjects whom the Investigator believes to be medically unfit to receive the study medication, or unsuitable for any other reason.

Treatment Schedule (Procedure): The volume to be administered will be up to 8 mL in a 10 mL syringe; up to 14 mL in a 15 mL syringe; or up to 17 mL in a 20 mL syringe. The oxycodone hydrochloride injection will be diluted with as small a volume as possible of sterile 0.9% saline, sterile 5% dextrose or sterile water for injection to provide the required dosage at a concentration of 25-50 mg/mL. The dosage of study medication for each subject will be calculated by the Investigator based on the individual subject's previous opioid use and current analgesia requirements.

Criteria for Evaluation:

Analysis Populations:

Enrolled Population - The enrolled population is the group of individuals who provided informed consent.

Safety Population - The safety population is the group of subjects who received at least one dose of study drug and had at least one post-dose safety measurement.

Efficacy Assessment(s):

There are no efficacy measurements for this study.

Safety Assessments:

Safety will be assessed by documentation of frequency and type of spontaneously reported adverse events and adverse events recorded after assessment of the infusion site. Vital signs will be carried out pre-treatment and at the end of the treatment.

Adverse Events

The subjects' volunteered symptoms and adverse events (AEs) will be recorded by spontaneous reporting throughout the study and at each infusion site assessment (every 24 hours and each time the infusion is re-sited) using the standard AE CRF page.

Vital Signs

Vital signs – weight, height will be recorded at study entry only, temperature, blood pressure, respiration rate and pulse rate will be recorded at screening and completion/discontinuation.

Infusion Site Assessments

An assessment of the infusion site will be recorded every 24 hours and every time the infusion is re-sited. The site will be assessed as normal or abnormal. Any abnormalities, e.g. signs/symptoms of inflammation, will be recorded as adverse events.

Serious Adverse Events

These will be recorded on the standard SAE data form.

Study Status: 33/50 patients recruited. All sites in the UK. LPLV was 29 May 2009. Analysis is underway and CSR is due in December 2009.

7.2.2 Non-clinical Studies

There were no ongoing company sponsored non-clinical studies during the reporting interval of 13 April 2009 - 12 October 2009.

7.3 Published Safety Studies

Nine (9) studies were published in the medical literature in the Chinese National Knowledge Infrastructure (CNKI) during the reporting period. Literature searches using CNKI were conducted for articles related to oxycodone. The summaries are listed below.

Xia Zhang , Xin-Jian Ruan , Chang Liu and Zhong-He Yu. Effect of vaginal administration of controlled-release oxycodone on cancer pain. Chinese Journal of Cancer 2009, 28, (7): 740-742

Objective: Controlled-release oxycodone is an orally administered strong opioid analgesic for moderate to severe cancer pain. Sometimes, its oral administration has to be stopped because of continuous nausea, vomiting, conscious disturbance, or inability to swallow. This study was to investigate analgesic effect of vaginal administration of controlled-release oxycodone on cancer pain and observe adverse events to provide a new choice for female patients who cannot tolerate the adverse events caused by oral administration.
Methods: Controlled-release oxycodone tablets were vaginally administered to 36 female patients with moderate to severe cancer pain. The initial dose was 10 mg every 12 h to patients who had never taken opioid analgesics; former dose continued to patients switching to vaginal route from oral route.
Results: Among the 36 patients, six had complete relief of cancer pain, 20 had significant relief, four had moderate relief, and four had slight relief, two had no relief. The relief rate of cancer pain was 83.3%. The mean time for onset of analgesic effect was 49 min; the mean duration of analgesic effect was 13.8h. Main adverse event was vaginal burning sensation in nine (25.0%) patients. No patient discontinued vaginal administration because of adverse events.
Conclusion: The vaginal administration of controlled-release oxycodone is a safe, effective and simple means of managing cancer pain in female patients who cannot tolerate the adverse events caused by oral administration.

Lin Haifeng, Wang Chaoying, Wang Xiugui. Clinical practice of oxycodone hydrochloride controlled-release tablets in the treatment of stomatitis with Ⅲ ~ Ⅵ grade induced by chemotherapy. J Fourth Mil Med Univ 2009, 30 (11)

Objective: To evaluate the efficacy of oxycodone hydrochloride controlled-release tablets in the treatment of stomatitis with III ~ VI grade induced by Chemotherapy.
Methods: 60 patients were randomly distributed to test and control groups. The test group was given regular treatment as well as oral oxycodone controlled-release tablet administration. And control group was given regular treatment.
Results: By SPSS software, χ^2 test was used between groups, and pain of all patients was controlled exclude 1 case. 20 cases in control groups (66.6%) had still moderate and severe pain ($P < 0.01$). Eating situation in the test group was improved and unable to eat (refer to be unable to eat semi liquid) was in 5 cases (16.6%). On the other hand, unable to eat in control group was only in 20 cases (66.6%) ($P < 0.01$). Loss rate of weight after coalescence of dental ulcer was more than 5%, and in the test group, 2 cases (6.6%) and control group, 13 cases (43.3%) ($P < 0.01$). Meso-recovering time between groups had no statistical significance.
Conclusion: Oxycodone controlled-release tablets in the treatment of stomatitis with III ~ VI grade induced by Chemotherapy are effective.

WU Xiao-nan, ZHAO Yun-bo, DING Li, WU Jian-yu, ZHANG Ping, CHENG Gang. Clinical efficacy and safety of Oxycontin in 85 patients with moderate and severe cancer pain. Chinese Journal of New Drugs 2009, 18 (8)

Objective: To evaluate the dose titration, adverse event and impact on life quality of OxyContin (controlled release tablets of oxycodone hydrochloride) in treating the late stage cancer pain.
Methods: OxyContin was administered and titrated in 85 patients whose numerical rating scale≥4. The dose titration and length of time needed to attain stable pain control were evaluated. Adverse event and quality of life (QOL) were assessed.
Results: Of the patients, 82 patients finished at least one cycle of titration and had effective pain control. The analgesic effect of 68 patients (82.9%) began within 60 min and mean time was 46. 3min. The titration time of 73 patients (89. 0%) was within 3 days and mean time was 2. 0 days. The analgesic effect maintained up to 12 h in 78 patients (95.1%). The minimal daily dose of OxyContin was 5mg and the maximal was 800mg. At least one adverse event occurred in 49 patients (59. 8%). The main adverse events included constipation (49. 4%), vomiting or nausea (10. 6%), dysuria (4.7%) and dizziness (5.9%), which could be tolerated by most of patients after symptomatic treatment. The incidence of adverse events was more frequent in female. No drug addiction was observed. The QOL of patients was significantly improved ($P < 0.01$).
Conclusion: Oxycontin is effective and safe in the treatment of cancer patients with moderate and severe pain. The adverse events can be tolerated, and the QOL of patients can be significantly improved.

Xia Zhenhua. The influence of efficacy of OxyContin in the treatment of 322 patients with moderate and severe tumor pain intervened by nursing. Chin J Misdiagn 2009 Vol 9 No. 14

Objective: To observe the influence of appropriate nursing to the efficacy and adverse reaction of OxyContin in the treatment of cancer patients with moderate and severe pain.
Methods: 322 patients were given OxyContin by oral administration, and combined with instruction of correct administration, drug prevention, psychological intervention and food instruction.
Results: CR+PR was in 310 cases, MR in 9 cases and NR in 3 cases. Adverse drug reactions with low incidence were as follows: nausea and vomiting, constipation, dizziness, weakness etc.
Conclusion: OxyContin administration combined with proper nursing can effectively control cancer pain and improve life quality and adverse drug reactions are mild with low incidence.

LI Lin, XU Chongan, XU Jie. Therapeutic effect of OxyContin on moderate and severe cancer pain. Practical Pharmacy And Clinical Remedies 2009, Vol 12 No. 2

Objective: To observe the analgesic effect and main side effects of OxyContin on moderate and severe cancer pain.
Methods: 72 patients were administered with OxyContin. The dose was 10mg /12h at the beginning, and it was adjusted according to the extent of pain. The therapeutic effect, KPS and side effects were observed.
Results: The mean onset time of analgesic effect was 45min, and the mean duration of analgesic effect was 12.13h. RR was 95.18%, CR was 65.12%, PR was 30.16%. The adverse effect was slightly.
Conclusion: OxyContin is safe and effective, and it has short response time and comparatively slight adverse effects in treatment of the moderate and severe cancer pain.

Liu Congmin, Wang Songmei. Clinical observation of efficacy of OxyContin in the treatment of cancer pain in the late phase by rectal administration. Drug and clinic 2009, Vol 47 No.11

Objective: To discuss the influence of OxyContin in the treatment of cancer pain in the late phase by rectal administration, a new way of administration.
Methods: 44 cancer patients in the late phase with tumor pain were given OxyContin by rectal administration and were clustered once before administration and efficacy and side effects were observed.
Results: Among 44 patients treated by OxyContin, effective rate of was 95.5%, and main side effects included constipation, nausea and Vomiting.
Conclusion: The method of OxyContin being administrated by rectums is simple, absorbed quickly, side effects are less and is worthy of trying in the clinic.

Li Ning, Li Hongxia. Efficacy of OxyContin in the treatment of moderate and severe tumor pain. Journal of Medical Forum 2009, Vol 30 No. 8

Objective: To observe the efficacy and safety of OxyContin in the treatment of moderate and severe tumor pain

Methods: 38 patients with moderate or severe tumor were given OxyContin in accordance with evaluating the changes of pain and life quality scale before and after treatment, and adverse drug reaction observed.
Results: Among 38 patients with moderate and severe tumor pain, 2 patients were mildly released (51.26%), 6, moderately (15.179), 17 significantly (44.174) and 13 fully released (34.121). Effective rate of the patients with moderate tumor pain was 100%, that of patients with severe tumor pain was 93.110 and total effective rate was 94.174. Pain scale before treatment was (71.96±11.21), and after treatment, 2106 ±1107 (P < 0101). Average Karnofskyll KPS scale before treatment was (55.102 ±11.138), and after treatment, 69.169 ±11.133, and life quality was dramatically improved after treatment (P < 0.101). Adverse drug reaction was as below: constipation in 8 cases, nausea and Vomiting in 4 cases, anorexia in 1 case, lethargy in 1 case and dizziness in 1 case.
Conclusion: Efficacy of OxyContin in the treatment of moderate and severe tumor pain is significant, adverse drug reaction is mild and can be administrated safely and can heavily improve the life quality of patients with cancers.

JIANG Peidi, YU Li, WU Yanfang. Efficacy of OxyContin in the treatment of advanced tumor pain. Chin J Clin Oncol Rehabil 2009, Vol 16 No. 3

Objective: To observe the efficacy and toxicity of OxyContin in the treatment of 82 advanced tumor patients.
Methods: Different doses of oral OxyContin were given to outpatients and in patients with advanced tumors in accordance with the principles of the three analgesic ladder, and their short term efficacy and toxicity were observed.
Results: Seventy-two of the 82 patients were effective after taking OxyContin, with minimal daily dose of 40 mg and maximal daily dose of 720 mg. The total effective rate of oxycontin was 87.18%. The toxicity was as follows: nausea in 7 cases, abdominal distension with constipation in 28 patients, dizziness in 3 cases, somnolence in 2 cases, skin rashes in 3 cases, mouth dryness in 3 cases.
Conclusion: OxyContin can be taken as one of the first preferred oral drugs for treatment of advanced tumor patients with severe pain.

LIU Yong, XIE Bin, CHENG Bao-zhi, WANG Ping, WANG Tao, HU Chuan-peng, LV Xia-zhi. Clinical observation of OxyContin in management of moderate and severe cancer pain. Modern Oncology 2009, 17 (07): 1335 – 1337

Objective: To observe analgesic effect and main side effects of OxyContin in management of the moderate and severe cancer pain.
Methods: Forty-nine patients with moderate and severe cancer pain were selected. OxyContin was administered at an initial dose of 10mg every 12h and titrated upwards according to the extent of pain relief. Outcomes included analgesic effect, Karnofsky Performance Status Scales (KPS) and side effect.
Results: Among all the 49 patients the mean duration of analgesic effect was 12. 45h, total effective rate was 89. 80%, effective rate of the moderate and severe cancer pain was 93.75% and 87.88%, respectively. KPS was elevated in 2 8 patients (57. 14%) and stable in 19 (38. 78%) after application of OxyContin, 2 patients (4. 08%) died. Main adverse effect was constipation in 7 patients (14. 29%).

Conclusion: OxyContin is safe and effective and with slight adverse effects in treatment of moderate and sever cancer pain.

7.4 Review of Scientific Literature

Literature searches using EMBase and MEDLINE, and PharmaSearch were conducted for articles related to oxycodone. Publications containing relevant scientific information are included in alphabetical order by author in the listing in Appendix VIIa.

7.4.1 Published Studies/Abstracts Containing Safety Information

Back, S. Prescription opioid aberrant behaviors – A pilot study of sex differences. Clin J Pain 2009;25(6):477-84.

OBJECTIVES: Patients who are prescribed opioids often display 1 or more aberrant prescription use behaviors (e.g., requesting early refills, borrowing medication from family), which raise concern among healthcare professionals. Little is known about the sex differences in specific types of aberrant behaviors or sex-specific predictors of such behaviors. The current study is aimed to begin addressing this gap in the literature.

METHODS: A battery of anonymous, self-report assessments was administered to 121 (49 men, 72 women) chronic pain patients enrolled in an outpatient pain management clinic. Most of the participants were white women with an average age of 51.6 years (SD=13.2).

RESULTS: Significantly more men than women were taking a prescribed opioid (91.7% vs. 77.8%, P=0.05). Women were significantly more likely than men to hoard unused medication (67.6% vs. 47.7%, P=0.04) and to use additional medications to enhance the effectiveness of pain medication (38.8% vs. 20.0%, P=0.04). A trend toward men using alternative routes of administration (e.g., crushing and snorting pills) more often than women was observed (8.9% vs. 1.5%, P=0.08). Among men, high rates of aberrant prescription use behaviors were associated with current alcohol use and the use of oxycodone and morphine. Among women, use of hydrocodone was associated with high rates of aberrant prescription use behaviors.

DISCUSSION: Some aberrant prescription use behaviors are common among chronic pain patients and may be sex-specific. Predictors of aberrant prescription use behaviors may also differ by sex. Additional research is needed to help identify aberrant prescription use behaviors that best predict sex-specific risk for developing opioid abuse or dependence.

MAH Comment: Additional research is needed to help elucidate aberrant prescription use behaviors that reliably predict sex-specific risk for developing opioid abuse or dependence and to determine the clinical implications of these findings.

Jannetto, P. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. Pharmacogenomics 2009;10(7):1157-67.

AIMS: The use of medication in pain management currently involves empirical adjustment based on observed clinical outcome and the presence of adverse drug reactions. In this study, pharmacogenomics and therapeutic drug monitoring were used to evaluate the clinical effectiveness of genotyping chronic pain patients on analgesic therapy. It was hypothesized that patients who have inherited polymorphisms in CYP2D6 that make them poor or intermediate metabolizers of opioid medications would have higher steady-state concentrations of those opioids and may be more likely to experience adverse drug reactions.

MATERIALS & METHODS: In an attempt to investigate the relationship between the polymorphic enzymes, steady-state drug concentrations, therapeutic effects and side effects, 61 patients were clinically evaluated and genotyped, and drug concentrations were measured and outcomes analyzed. Samples were collected and DNA extracted from whole blood using a Puregene(R) DNA isolation kit. CYP2D6 genotyping (*3, *4, *5, *6, *7, *8 and gene duplication) were carried out using Pyrosequencing(R). Steady-state plasma concentrations of methadone, oxycodone, hydrocodone and tramadol were determined by HPLC tandem mass spectrometry.

RESULTS: The results demonstrated the prevalence of CYP2D6 polymorphisms in the population undergoing pain management was not statistically different from the general population. The majority of the pain patients (54%) were extensive metabolizers; 41% were intermediate metabolizers and 5% poor metabolizers. Poor metabolizers in general tended to have the highest steady-state drug concentrations compared with extensive metabolizers (poor metabolizers > intermediate metabolizers > extensive metabolizers) although this wasn't statistically significant. Also, a relationship between oxycodone steady-state drug concentrations and pain relief was found. A total of 80% of patients reporting adverse drug reactions also had impaired CYP2D6 metabolism. The remaining 20% with adverse drug reactions had other cofactors (i.e., drug-drug interactions) that could explain the toxicity.

CONCLUSION: These results suggest that patient care may be improved by genotyping and following therapeutic drug concentrations. Benefits include increased efficiency in proper drug selection, dose optimization and minimization of adverse drug reactions to improve patient outcome and safety. In addition, this study clearly demonstrated a relationship between oxycodone steady-state drug concentrations and pain relief. Future large-scale prospective studies are needed to confirm the clinical value of using genetic information to guide pain management therapy.

MAH Comment: As stated by the authors, additional large-scale prospective studies are needed to confirm the clinical relevance of their findings and to elucidate the clinical implications of using genetic information to guide pain management therapy.

Nieminen, TH. Rifampin greatly reduces the plasma concentration of intravenous and oral oxycodone. Anesthesiology 2009;110(6):1371-8.

BACKGROUND: Oxycodone is a mu-opioid receptor agonist that is metabolized mainly in the liver by cytochrome P450 3A and 2D6 enzymes. Rifampin is a strong inducer of several drug-metabolizing enzymes. The authors studied the interaction of rifampin with oxycodone. Their hypo-

thesis was that rifampin enhances the CYP3A-mediated metabolism of oxycodone and attenuates its pharmacologic effect.

METHODS: The protocol was a four-session, paired crossover. Twelve volunteers were given 600 mg oral rifampin or placebo once daily for 7 days. Oxycodone was given on day 6. In the first part of the study, 0.1 mg/kg oxycodone hydrochloride was given intravenously. In the second part of the study, 15 mg oxycodone hydrochloride was given orally. Concentrations of oxycodone and its metabolites noroxycodone, oxymorphone, and noroxymorphone were determined for 48 h. Psychomotor effects were characterized for 12 h by several visual analog scales. Analgesic effects were characterized by measuring the heat pain threshold and cold pain sensitivity. RESULTS: Rifampin decreased the area under the oxycodone concentration-time curve of intravenous and oral oxycodone by 53% and 86%, respectively ($P < 0.001$). Oral bioavailability of oxycodone was decreased from 69% to 21% ($P < 0.001$). Rifampin greatly increased the plasma metabolite-to-parent drug ratios for noroxycodone and noroxymorphone ($P < 0.001$). Pharmacologic effects of oral oxycodone were attenuated.

CONCLUSIONS: Induction of cytochrome P450 3A by rifampin reduced the area under the oxycodone concentration-time curve of intravenous and oral oxycodone. The pharmacologic effects of oxycodone were modestly attenuated. To maintain adequate analgesia, dose adjustment of oxycodone may be necessary, when used concomitantly with rifampin.

MAH Comment: As previously mentioned, Section 4.5, Drug Interactions, of the oxycodone CCDS has been updated and currently states: "Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly." The recent findings from the scientific literature are adequately reflected in the present version of the oxycodone CCDS.

Richards, P. Two exploratory double-blind crossover studies of the treatment of chronic noncancer pain: efficacy and safety of concurrent dosing of morphine plus oxycodone vs. morphine alone. Journal of Pain 2009;10(Suppl1)(S49): Abstr 298.

Animal studies have shown that co administration of morphine and oxycodone (M+O) produced synergistic reductions in acute pain with minimal AEs. Two double-blind, randomized, crossover studies in patients with chronic, moderate-to-severe, noncancer pain (Study A, N = 21; Study B, N = 23) evaluated the efficacy and safety of concurrent oral dosing of M+O (liquid formulation) at fixed ratios (Study A, 3:2; Study B, 1:2) vs. equi-analgesic doses of oral liquid morphine. Period 1: randomized patients received flexible M+O or morphine alone q4h for 3-7 days to achieve steady-state pain relief. Period 2: patients received alternate treatment (no washout). Rescue medication was study medication at 25% of the randomized dose. In both studies, M+O and morphine alone achieved similar analgesic efficacy. However, Study A patients achieved equi-analgesic effects using (mean±SD) 40.5±28.4 mg/day (36%) less morphine equivalents with M+O vs. morphine alone ($P < 0.006$). Study B patients achieved equi-analgesic effects using 20.5±20.9 mg/day (31.9%) less morphine equivalents with M+O vs. morphine alone ($P = 0.0026$). There were no unusual AEs seen with M+O. M+O was associated with less nausea (Study A: $P < 0.05$), less constipation (Study B: $P = 0.025$), and less drowsiness (Study A, Days 2, 3, & 5: $P < 0.05$) vs.

morphine alone. Pooled analysis showed 1.5 times greater risk of constipation with morphine alone vs. M+O (P < 0.044; RR = 1.554; 95% CI = 1.000-2.418) and a trend toward greater risk of drowsiness with morphine alone (P = 0.154; RR = 1.363, 95% CI =.887-2.094). M+O was well tolerated and provided equi-analgesic pain relief at significantly lower morphine-equivalent doses vs. morphine alone.

MAH Comment: This article suggests that use of morphine and oxycodone provides analgesic pain relief at significantly lower morphine equivalent doses vs. morphine alone as well as diminishing the risk of constipation. This study suggests synergistic reduction in humans as well as in animals with the use of both drugs. Additional research is necessary to confirm the findings and elucidate the clinical implications.

7.4.2 Non-clinical Published Studies/Abstracts Containing Safety Information

A review of the published literature relevant to the nonclinical pharmacology, toxicology, pharmacokinetics and drug metabolism of oxycodone hydrochloride was conducted using MedLine, EMBASE and Pharma Search for the reporting period 13 April 2009 through 12 October 2009. No new report or summary of published literature containing relevant information on the pharmacology, toxicology, pharmacokinetics or drug metabolism of oxycodone hydrochloride was found.

8. OTHER INFORMATION

8.1. Risk Management

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System has been discussed in detail in several previous PSURs. As reported in PSUR 12 (Oct 2005 – Apr 2006), on 1 January 2006 operation and control of this program was assumed by the Denver Health and Hospital Authority (DHHA). Purdue Pharma L.P. uses information from the RADARS® System to inform its risk management activities. RADARS® System data is included in the 2008 Annual Summary Report of the OxyContin® Tablets Risk Management Program dated October 2009. The Executive Summary of this report is located in Appendix IXc. Aggregate data from the RADARS® system will continue to be monitored and any pertinent information affecting the safety profile for oxycodone will be presented in future PSURs.

8.2. Efficacy-Related Information

A MedDRA SMQ query for lack of effect was performed with additional events such as pain, inadequate analgesia, metastatic pain, inflammatory pain, discomfort, and breakthrough pain. The search revealed 63 cases of which 30 originated from US litigation sources. Preferred terms in these 63 cases included the following 95 events: pain (N=38); drug ineffective (N=19); inadequate analgesia (N=19); drug effect decreased (N=7); drug tolerance (N=7); breakthrough pain (N=4); and, drug effect delayed (N=1). These events suggesting a possible lack of effect with opioid

therapy may be influenced by many factors, including exacerbation or progression of the patient's underlying conditions requiring dosage adjustments (titration), such as cancer or arthritis, increased physical activity, and/or the development of drug tolerance. There is no information currently available that would indicate any specific issues with lack of efficacy for the oxycodone preparations included in this PSUR.

8.3. Late Breaking Information

None.

9. OVERALL SAFETY EVALUATION

This is the 19th PSUR for oxycodone and includes information received from 13 April 2009 through 12 October 2009. Units equaling a total of about 7,813,224 patient months of exposure were distributed in the reference period. This is less than the 8,779,809 patient months reported in the previous reference period and is possibly due to a decrease in the market share of OxyContin® drug sales. In addition to the market patient exposure data, patients are being exposed in a number of ongoing clinical studies involving oxycodone.

The Purdue/Mundipharma/Napp (PMN) companies Drug Safety and Pharmacovigilance Departments received or created 2,394 cases, initial and follow-up reports, from worldwide sources reporting events temporally associated with an oxycodone-containing product. This number is slightly increased as compared to the number of cases received / created during the last reporting interval (2,342). Given the decreased patient exposure, the overall reporting rate for the period has increased. The increase is due to the increased number of cases received through US litigation cases during the current period (714 cases) as compared to the previous reporting period (397 cases). The number of non-litigation cases received (1,680) was in fact lower than that received (1,945) during the last reporting interval.

This PSUR summarizes the safety data from the 432 cases that met ICH E2C inclusion criteria. This number is decreased as compared to the number of cases that met inclusion criteria for the last reporting period (766). This decreased number of cases is partially secondary to a decreased number of legal cases (48 versus 266) that met inclusion criteria for the PSUR. Of the 432 reports included in this PSUR, 366 were initial reports and 66 follow-up. The majority of the cases, 311 (72%) originated in the USA. Of the (48) litigation cases (20 initial and 28 follow-up reports), all originated in the US. Forty (40) of the 48 US litigation cases contained at least one event consistent with drug abuse, drug dependence, drug addiction, withdrawal and/or overdose.

Events derived from legal cases may not have the same significance as those from "usual" spontaneous reports as the events included in cases of this type were not necessarily reported by a healthcare professional as a suspected adverse event for oxycodone. Therefore, legal cases are discussed only exceptionally, when deemed clinically appropriate. Medical review of the legal cases received during the reporting period did not identify any new issues attributable to oxycodone.

9.1. Principal Findings

Adverse event report characteristics

Of the overall total of 432 cases:

- 381 / 432 cases were classified as serious
- 51 / 432 cases were classified as non-serious
- 97 / 432 cases were associated with a fatal outcome
- 69 / 432 cases involved a report of overdose, 50 of which were fatal
- 206 / 432 involved reports of drug abuse, drug dependence, drug addiction and/or withdrawal, 42 of which had a fatal outcome

The summary tabulation of the 432 cases (Appendix Vb) included 1,268 adverse events; 706 (56%) of which were considered serious and 562 (44%) non-serious. Of the 706 serious events, 200 (28%) were unlisted; and of the 562 non serious events, 234 (42%) were unlisted. Consistent with previous PSURs, the majority of reports, including those discussed in section 6.4 (individual case presentation), describe either well-known pharmacological effects of opioids (including abuse and overdose with or without a fatal outcome), adverse effects known to be associated with oxycodone and listed in the CCDS, or events without likely causal association with oxycodone but that occur commonly in the patient population taking oxycodone for chronic pain. The information in this PSUR does not indicate any change in the characteristics of listed reactions.

Cumulative review of the serious unlisted reactions shown in Appendix VI also does not suggest any new risks potentially attributable to oxycodone. The event terms in Appendix VI comprise a mixture of isolated reports, known or anticipated effects of oxycodone (e.g. complications of CNS or respiratory depression), and events with no evidence of association with oxycodone that are clinically expected in the patient population exposed to oxycodone for therapeutic or non-therapeutic reasons.

Oxycodone is available in immediate and controlled-release oral formulations, and for intravenous use. Sixteen (16) of the 462 cases involved an immediate-release formulation as the lone oxycodone containing suspect medication (i.e. without a controlled-release oxycodone co-suspect medication). Due to the small number of cases, analysis of the safety profile of immediate release formulations as compared to controlled release formulations is difficult. Medical evaluation of these cases did not reveal any evidence of a specific risk associated with the immediate-release formulations.

9.2. Death and Cases with a Fatal Outcome

There were 97 fatal cases in this PSUR. Forty-two (42) of the fatal cases were associated with at least one term associated with drug abuse, drug dependence, drug addiction, and withdrawal, all of which originated in the USA.

Fifty (50) fatal cases were associated with an overdose term; all but 2 originated in the USA. The reports in this PSUR of fatal overdose involving oxycodone (N=50), either alone or in association with other medications and/or substances of abuse, did not reveal any new issues. Table VI displays the preferred terms that were included in the fatal overdose cases.

Table VI
Overdose Cases with Fatal Outcome Breakdown by PT* (N=50)

Preferred Term	Total Count
Overdose	12
Accidental Overdose	10
Multiple drug overdose	9
Multiple drug overdose accidental	16
Multiple drug overdose intentional	4

*Individual cases may contain more than one event per case

Of the remaining 47 fatal cases not associated with an overdose, 29 contained sufficient information to ascertain a probable cause of death and 18 did not explicitly report the cause of death or the cause of death was unknown (PT = death). The primary events for the 29 cases with a reported or ascertainable cause of death are listed below in Table VII.

Table VII
Primary PT for Cases with a Reported / Ascertainable Cause of Death

Primary PT	Total Count
Drug abuse	4
Drug dependence	4
Completed suicide	3
Sepsis	2
Arrhythmia	1
Cardiorespiratory arrest	1
Myocardial infarction	1
Ileus	1
Symptom masked [myocardial infarction]	1
Drug toxicity	1
Road traffic accident	1
Cachexia	1
Malignant neoplasm progression	1
Pancreatic carcinoma	1
Intentional drug misuse	1
Substance abuse	1

Table VII Primary PT for Cases with a Reported / Ascertainable Cause of Death	
Primary PT	**Total Count**
Pulmonary embolism	1
Pulmonary oedema	1
Arteriosclerosis coronary artery	1
Non-small cell lung cancer	1
Total	**29**

All of the 29 cases with a reported or ascertainable cause of death had alternative explanations for the fatal outcome (unrelated to oxycodone therapy) such as pre-existing malignancies, cardiovascular disease and/or risk factors, or were associated with abuse, misuse or accidental intake. In the case of ileus (GBR-2009-0005314), the investigator reported the ileus as due to the progression of disease (peritonitis carcinomatosa). The cases involving arrhythmia (GBR-2009-0005639) and cardiorespiratory arrest (MAG-2009-0001070) are discussed above in Section 6.4 (individual case presentation). The cases involving completed suicide are discussed further in Section 9.4 Suicide and Suicidal Ideation Cases below.

The 19 cases involving the PT of death included 1 non fatal case of a near death experience that was not further specified. The remaining 18 cases contained plausible alternative etiologies for the fatal outcome (e.g. underlying malignancies or heart failure), involved a possible (unreported, uncoded) overdose, reported drug abuse, or contained limited information beyond that a patient using oxycodone had died making it impossible to draw any conclusion regarding the role, if any, of oxycodone.

The review of the fatal cases in this PSUR did not reveal any new safety issues for oxycodone.

9.3. Drug Overdose

Adverse events related to drug overdose were reported in 69 cases.

- 50 / 69 of the cases reported a fatal outcome.
- 19 / 69 of the cases reported a non-fatal outcome.
- 65 / 69 of the cases originated in the USA
- 48 / 65 of the cases that originated in the USA were fatal.
- 4 / 69 of the cases originated outside the USA.
- 2 / 4 of the cases that originated outside the USA were fatal.
- 14 / 69 originated from US litigation report sources
- 55 / 69 originated from non-litigation sources

The preferred terms for the 19 cases with a non-fatal outcome are presented in Table VIII below:

Table VIII Overdose Cases with Non-fatal Outcome Breakdown by PT (N=19)	
Preferred Term	**Total Count**
Overdose	15
Accidental Overdose	1
Multiple drug overdose	3

Of the 19 cases with a non-fatal outcome, 17 originated in the USA, including 3 from US litigation activities.

The review of these cases did not reveal any new issues regarding the occurrence of drug overdose in patients treated with oxycodone.

9.4. Drug Abuse, Drug Addiction, Drug Dependence and Withdrawal

Adverse events related to drug abuse, drug dependence, drug addiction or withdrawal was reported in 206 cases. One hundred eighty-five (185) of the 206 cases originated in the USA, including 34 cases that originated from US litigation report sources. Table IX displays the PTs terms in the 206 cases.

Table IX Drug Abuse, Drug Dependence, Drug Addiction, or Drug Withdrawal Cases by PT*	
Preferred Term	**Total Count**
Drug abuse	91
Drug dependence	81
Drug withdrawal syndrome	33
Intentional drug misuse	32
Substance abuse	24
Drug detoxification	6
Withdrawal syndrome	4
Drug abuser	3
Dependence	1
Drug withdrawal syndrome neonatal	1

*Individual cases may contain more than one event per case

Forty-two (42) of the 206 cases reported a fatal outcome. All of these 42 cases originated in the USA.

The review of these cases did not reveal any new issues regarding the occurrence of drug abuse, drug dependence, drug addiction, or withdrawal in patients treated with oxycodone, issues that are largely limited to the USA.

9.5. Suicide and Suicidal Ideation Cases

There were 20 cases involving the PT(s) completed suicide, multiple drug overdose intentional, suicidal ideation, and suicide attempt. Table X, below, lists the PTs for all 20 cases.

Table X
Suicide and Suicidal Ideation Cases by PT

Suicidal ideation	9
Competed suicide	6
Multiple drug overdose intentional	4
Suicide attempt	1

Fourteen (14) of the 20 cases originated from US litigation sources. Five (5) of the 14 US litigation cases were fatal. USA-2009-0038824, involved a suicide with carbon monoxide poisoning in a paralyzed patient with a spinal disorder and depression. USA-2007-0027668, reported in a previous PSUR, involved a male patient with a history of drug dependence and drug abuse who committed suicide via a gunshot wound. USA-2009-0038815 involved a 34-year-old addicted, depressed male who committed suicide via a gunshot wound. The 2 remaining cases involved suicide via intentional multiple drug overdose involving methadone and citalopram in one case (USA-2009-0039042) and oxycodone, citalopram and valproic acid in the other case (LEG-2009-0006992).

The remaining 6 (non legal) cases are summarized below:

USA-2009-0038580 involved an intentional multiple drug overdose with OxyContin, fentanyl patch and numerous unspecified street drugs in a 46-year-old female with a history of pain, insomnia, depression and a suicide attempt.

USA-2009-0039838 involved a female patient who committed suicide by taking several OxyContin as well as 20 Lexapro tablets. The outcome was fatal. No further details provided.

USA-2009-0037533, reported in a past PSUR submission, involved a patient with multiple sclerosis and paraparesis who shot himself in the head.

USA-2009-0038684 involved a male patient who murdered a person and then committed suicide. No further details provided.

USA-2009-0038419 involved a male consumer who stole OxyContin from his roommates and committed suicide while taking OxyContin. No further details provided.

DEU-2009-0005086, reported in a past PSUR submission, involved a 70-year-old male with a neurological disorder who was admitted to the intensive care unit for medical observation following a suspected suicide attempt after ingesting approximately 200 Oxygesic (10mg and 20mg) tablets. The patient recovered.

As described in previous PSURs, persons using oxycodone for therapeutic or illegal purposes are prone to multiple risk factors for suicide, including severe chronic pain, terminal illnesses, and a variety of psychiatric disorders. The reports in this PSUR do not appear notably different from those previously presented and provide no evidence that treatment with oxycodone has any causal association with the risk of suicide.

9.6. Experiences in Special Patient Groups

9.6.1 Labor and Delivery

There are seven cases in this category.

USA-2008-0033436 (drug dependence), a US litigation case reported in a past PSUR submission, involved a female patient with Crohn's disease and ulcerative colitis with alleged injuries that included drug addiction, painful drug withdrawal, physical and mental pain and suffering, paranoia, delusional disorder, obsessive compulsive disorder and depression. The patient was taking OxyContin throughout the course of her pregnancy and underwent scheduled repeat caesarean section without complications, delivering a viable female infant with Apgars of 7 and 9. No additional information was available concerning the infant. According to the medical records, at various times she was taking more OxyContin than was prescribed.

MAH Comment: There was no report of any untoward drug effect related to the patient's pregnancy or offspring in the litigation case.

USA-2009-0037367 (drug dependence) involved a 28-year-old pregnant female who was involved in a fatal MVA while driving without her seatbelt. Her blood and urine were positive for oxycodone (serum level 124.1 ng/mL). The medical examiner indicated that she died as a result of multiple blunt force injuries and that her opiate dependence and oxycodone use may have been contributory.

MAH Comment: The CCDS warns that oxycodone may impair the ability to drive.

GBR-2009-0005404 (cognitive disorder) involved a patient with a history of a malignant neoplasm and neuropathic neck pain treated with OxyContin. When the patient became pregnant, her physician reduced her dose of OxyContin to 240mg (80mg three times a day) over a six month period. Following delivery of a female child at 41 weeks gestation, the pain team reduced the dose to 80mg twice daily as higher doses were causing cognitive impairment. The baby (**GBR-2009-0005445; drug detoxification)** was placed in the neonatal unit for 14 days for detoxification. There were no birth defects reported.

MAH Comment: Based on the available information, the causal role of oxycodone in the occurrence of the cognitive impairment cannot be excluded. Of note, thinking abnormal is a listed event in the oxycodone CCDS.

GBR-2009-0005468 (pain management) involved a 40-year-old female, 30 weeks pregnant, who was admitted to the hospital for pain management on oral oxycodone 120mg and oral OxyNorm 60 mg for back pain. At 34 weeks gestation, a female neonate was delivered by caesarean section due to the mother's back pain. No birth defects were noted. The baby (**GBR-2009-0005469)** was transferred to the neonatal unit to undergo an opioid detoxification regime for seven days.

USA-2009-0038137 (premature labor) involved a 20-year-old female who had been taking Opana ER (oxymorphone) 40 mg before and throughout her pregnancy. The patient experienced premature uterine contractions and was hospitalized for pre-term labor at 32 weeks gestation. The oxymorphone dosage had been reduced to half the week prior to admission. At 36 weeks gestation, she delivered via spontaneous vaginal delivery. The neonate **(USA-2009-0038138; premature baby)** developed opiate withdrawal symptoms (agitation, jerking movements even during sleep, tachypnea, and a high pitched cry) shortly after birth. Specialty lab results showed an oxymorphone value of 1,650 and oxycodone value of 123 (units not reported). The urine toxicology test was negative. Within 36 hours, the newborn's weight had decreased by appproximately12% from 3,010 gm to 2,635 gm. Her higher score on the neonatal abstinence scoring system (NAS) was 12. On the newborn's third day of life morphine 4 mg was initiated orally via bottle feedings for one week. The NAS score started to decline, but as of 10Feb2009 the NAS score was 8 and morphine was continued for a total of 11 days.

MAH Comment: Drug dependence and withdrawal are well known problems in infants exposed to opiates during pregnancy. The current oxycodone CCDS states the use of this product should be avoided to the extent possible in patients who are pregnant or lactating. In the cases of premature labor and premature birth, a contribution of oxycodone to the events cannot be ruled out. As Opana was the only prescribed medication reported, it is possible that the patient may have been taking non-prescribed oxycodone or illicit drugs. Additionally, the possibility of drug withdrawal, when the Opana ER dosage was reduced, could also present a plausible alternative explanation.

In summary, the review of the cases involving terms of labor and delivery included in this PSUR did not reveal any new issues or risks.

9.6.2 Pediatric Cases

Twelve (12) cases described exposures and/or other adverse events in patients 18 years of age or younger; 10 cases originated in the US and 2 cases originated in the United Kingdom. The cases are summarized below.

There were 3 cases in neonates less than one month old:

GBR-2009-0005445 (drug detoxification), GBR-2009-0005469 (drug withdrawal syndrome neonatal) and **USA-2009-0038138 (premature baby)** are discussed above in Section 9.6.1 Labor and Delivery.

MAH Comment: Drug dependence and withdrawal are well known problems in infants exposed to opiates during pregnancy. The current oxycodone CCDS states the use of this product should be avoided to the extent possible in patients who are pregnant or lactating.

There were 3 (fatal) cases in children 1 year to less than 13 years old:

USA-2009-0037888 (drug toxicity, accidental drug intake by child), initially reported via the news media, involved a 3-year-old female who died of drug toxicity of unknown etiology. The post mortem blood screen was positive for diazepam and oxycodone. The urine screen was positive for nordiazepam, temazepam, and oxycodone.

USA-2009-0039234 (overdose), reported via the news media, involved an 11-year-old female who died from an apparent overdose after ingesting up to 5 oxycodone pills prescribed for a family member. The case was under police investigation regarding the manner of overdose.

USA-2008-0034472 (anoxic encephalopathy), initially reported from the news media, involved a 21-month-old child who died 4 months after taking OxyContin. Alprazolam, marijuana plants, and OxyContin were found at the parent's home. The final diagnoses included anoxic/ischemic encephalopathy, brain with cortical necrosis and infarcted white matter.

MAH Comment: Accidental exposures are a serious issue for children for all drugs, including oxycodone. Precautions concerning keeping the medication out of reach of children are found in local labeling.

There were 6 cases involving adolescents (13 years to less than 18 years old):

USA-2009-0039140 (death) involved an adolescent who took his relatives OxyContin and passed away. No further information was provided.

USA-2009-0039182 (accidental overdose), received initially from the news media, involved a 14-year-old male who was seen consuming alcohol and an unknown pill. He was found dead, from a drug overdose involving oxycodone, nicotine, sertraline, and marijuana.

USA-2009-0037653 (multiple drug overdose accidental) involved a 17-year-old male who died from a combination of OxyContin, alprazolam, and morphine.

USA-2009-0039181 (overdose) involved a 15-year-old female who was hospitalized in a coma from an overdose of OxyContin.

USA-2009-0037594 (drug abuse), reported in the past PSUR, involved a 16-year-old male patient who purchased OxyContin on the street for about 2 years. He wanted to stop and experienced withdrawal symptoms.

USA-2009-0039327 (drug dependence) involved a 17-year-old adolescent female who was buying OxyContin on the street and had become addicted to it.

MAH Comment: Drug abuse, dependence, and overdose involving adolescents remains a significant issue, largely limited to the USA.

The review of the pediatric cases included in this PSUR did not reveal any new issues or risks.

9.7 Potential Drug Interactions

There were 3 cases involving reported drug interactions during the review period.

GBR-2009-0005358 (drug interaction) refers to a 57-year-old male with hemochromatosis who had been treated with OxyContin (40mg twice daily) and developed withdrawal syndrome with sweating, pain and gastralgia 3 days after initiating pristinamycin. The reporting pharmacist considered a drug interaction between the two drugs. Pristinamycin was withdrawn 3 days later and the patient recovered.

MAH Comment: There are no known interactions between streptogramin antibiotics and opiates. There is insufficient information to allow a determination of what may have precipitated the withdrawal reaction in this patient. A plausible alternative explanation is that the patient may have suffered a reaction to the antibiotic.

GBR-2009-0005565 (drug interaction) involved a 39-year-old man on pregabalin (300mg daily) for chronic pain from mixed connective tissue disease. Concomitant medication included amitriptyline 150mg daily and oxycodone 20mg daily. The patient was admitted to the hospital following a fall at home and was obtunded, hypoventilating, hypoxic and was found to have aspiration pneumonia. It was also reported that the patient had consumed 10-15 units of alcohol on the same day. The obtundation was felt to be due to a combination of alcohol, multiple central nervous system sedating drugs, and a probable head injury. It was felt that the combination of alcohol, Lyrica, amitriptyline, and oxycodone along with the fall and probable concussion were all jointly responsible for aspiration and hypoventilation. Pregabalin was discontinued and the patient recovered from the events.

USA-2009-0039983 (acute renal failure) involved a male patient who experienced excessive sedation attributed to an interaction between pregabalin and OxyContin. See Section 6.4 Individual Case Presentation, Renal and Urinary Disorders for additional details.

***MAH Comment** on the two above cases:* The oxycodone CCDS warns against the enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as alcohol, other opioids, sedatives, hypnotic, anti-depressants, sleeping aids, phenothiazines and neuroleptic drugs, etc.

In summary, the review of the drug interaction cases included in this PSUR did not reveal any new issues or risks.

9.8 Medication Errors

Medication error was reported in 17 cases, 5 of which reported a fatal outcome. Table XII below displays the preferred terms included in the 17 cases.

Table XII Medication Error Cases by PT* Distinct Cases N=17	
Preferred Term (PT)	**Total Count**
Wrong technique in drug usage process	5
Inappropriate schedule of drug administration	4
Accidental Drug Intake by Child	2
Incorrect dose administered	2
Incorrect route of drug administration	2
Drug Administration Error	1
Medication error	1
Drug Dispensing Error	1
Drug Prescribing Error	1
Total	19

*Individual cases may contain more than one event per case

The 2 cases involving accidental drug intake by child are discussed in Section 9.6.2 Paediatrics. The remaining 15 cases are presented below.

USA-2009-0038959 (wrong technique in drug usage process) involved a patient who crushed his OxyContin 30 mg tablets and put them down his NG (nasogastric) tube. He was getting adequate pain relief and was doing fine. The physician discontinued the drug.

USA-2009-0039147 (wrong technique in drug usage process, intentional drug misuse) involved a 42-year-old female who was prescribed OxyContin 20mg every 12 hours and was doubling her dose. She ran out of her prescription and took a friend's OxyContin 80mg tablet and cut it in half. No side effects or problems were reported.

USA-2009-0039820 (wrong technique in drug usage process) involved a female patient who was cutting her OxyContin in half and abusing them. The patient died as result of her medication abuse on an unspecified date.

USA-2009-0039953 (wrong technique in drug usage process) involved a male patient who was taking OxyContin 80mg for back pain without a prescription. He reportedly cut the 80mg tablet in half as it was too potent.

USA-2009-0037327 (wrong technique in drug usage process) involved a 70-year-old male with a history of chronic renal failure, chronic lymphocytic leukemia, and metastatic small cell bladder cancer with liver, lung, and retroperitoneal metastases who was chewing his medications, including OxyContin 40 mg every 12 hours, with applesauce. The patient would get very tired at times and at other times seemed extremely agitated.

USA-2009-0037656 (inappropriate schedule of drug administration) involved a patient who had been taking oxycodone/acetaminophen at a dose of 30-40 mg daily. The patient was

prescribed OxyContin 20 mg two times a day for an unspecified indication. The first dose of the medication was administered early afternoon, and the pharmacist incorrectly ordered and administered the second dose around 8 PM, 6 hours after the first dose. Two - three hours after taking the second dose of OxyContin, the patient experienced respiratory suppression. The patient was treated with Narcan (naloxone hydrochloride). The outcome of the events was reported to be recovered.

GBR-2009-0005194 (**inappropriate schedule of drug administration)** involved a 47-year-old male on an unspecified antihypertensive drug who was treated with OxyNorm and OxyContin for pain. For two to three weeks, the patient mistakenly took OxyNorm twice daily, and OxyContin capsules four to five times daily. On an unspecified date, the patient developed hypotension. No additional adverse events or signs of overdose were identified. The patient recovered on an unspecified date.

USA-2009-0038206 (drug dispensing error, inappropriate schedule of drug administration) involved an elderly male in his 70's who was prescribed OxyContin 10mg tablets [every 12 hours] but was given 40mg tablets by his pharmacy. He took two 40 mg OxyContin tablets in the evening and two 40 mg tablets in the morning, experienced respiratory arrest and died in the ER. According to the reporting physician, the cause of death was "respiratory arrest."

GBR-2009-0005275 (incorrect dose administered) involved a patient prescribed intravenous OxyNorm (oxycodone hydrochloride) 20mg/2ml daily. The nurse administering OxyNorm to the patient confused the concentration with the total quantity of oxycodone in the vial; therefore the patient received 40mg instead of 20mg with a syringe pump. As a result of the medication error the patient was given an overdose and experienced somnolence. The events resolved without sequelae.

USA-2009-0039528 (incorrect dose administered) involved a female patient who experienced a fatal overdose after she was inadvertently administered an extra (unspecified) dose of OxyContin.

USA-2009-0040411(incorrect route of drug administration) involved a patient crushing OxyContin and clonidine.

USA-2009-0040349 (incorrect route of drug administration) involved a patient crushing OxyContin and inserting it rectally. The outcome of the event crushing OxyContin and inserting it rectally was not reported.

USA-2009-0038116 (drug administration error) involved a patient taking OxyContin 10 mg twice daily, which was titrated to 20 mg twice daily. The patient's wife gave the patient two 10mg OxyContin twice daily. After refilling the prescription to 20 mg tablets, she inadvertently continued to give the patient 2 tablets twice daily until the error was discovered. The patient fell and sustained a head injury on an unspecified date. The outcome was recovered.

USA-2009-0039087 (medication error) involved a 66-year-old female who was taking oxycodone (dose 220mg) for an unspecified indication and experienced convulsions, consciousness

decreased, hypotension, hyperkalemia and [an unspecified] medication error (dosage). Oxycodone was discontinued and the patient recovered without sequelae.

USA-2009-0039475 (drug prescribing error) involved a 60-year-old opioid naïve female who was prescribed oxycodone 10mg q4h as needed for an unspecified indication. An unspecified period of time after oxycodone was initiated, the patient experienced hallucinations, nausea and vomiting. Oxycodone was discontinued and the patient recovered with 24-48 hours.

MAH Comment: The reported events of medication error contain multiple root causes, and do not indicate a single systemic source to which these medication errors can be attributed. Three (3) of the cases were associated with reports of drug abuse. The issue of inadequate analgesia and/or drug tolerance, whether or not specifically reported, may have been a precipitating factor for some of the other cases of medication errors. The Company will continue to monitor reports of medication error in patients treated with oxycodone.

9.9 Analysis of Individual Case Histories for Selected Adverse Events of Interest

9.9.1 Hepatic Dysfunction

Cases with terms describing potential hepatic dysfunction were reviewed.

USA-2009-0038181 (hepatitis) involved a female patient in her 40's who was taking OxyContin along with other unspecified medications and developed drug-induced hepatitis from OxyContin. According to the patient's physician, the patient had no known history of hepatitis, no evidence of hepatitis and no labs for hepatitis in her medical records.

USA-2009-0038947 (cirrhosis) was received via US litigation sources and involved a patient with a history of diabetes secondary to prednisone on insulin, neuropathy, hypertension, bladder cancer, coronary stents, bone infection, and back and neck surgeries who had been treated with OxyContin 80mg every 8 hours for pain with oxycodone (2) 15 mg tablets every 4 hours as needed. Beginning with the use of OxyContin, the patient experienced symptoms that have not yet resolved which include being suicidal, addiction (to OxyContin), cirrhosis of the liver, loss of memory, mood swings, falling multiple times, dizziness, depression, confusion, disorientation, constipation, fluid build-up, no sex life, insomnia, lethargic, and being unable to drive an automobile due to lethargy. No further information concerning the cirrhosis was reported.

MAH Comment: There is insufficient information to confirm the diagnoses and to assess the causal role of oxycodone (if any) in the latter 2 cases of hepatitis and cirrhosis.

DEU-2009-0005297 (ascites) involved a 73-year-old female with a history of pulmonary cancer, bronchial cancer, colon cancer (1981), hypertension, and neuropathic pain who was enrolled in a Company sponsored clinical trial OXN2001 (oxycodone/naloxone CR vs. oxycodone CR) and experienced worsening dyspnea, edema (legs) and ascites requiring two percutaneous punctures. Concomitant medication included atenolol, hydrochlorothiazide/lisinopril, dexamethasone and pregabaline. Study medication was discontinued following the hospitalization for the ascites. Two

weeks after the last dose of study medication, the patient died from an acute myocardial infarction. The investigator found all events to be unlikely related to the treatment with the study medication.

MAH Comment: Progression of the patient's underlying malignancy or probable underlying cardiac failure in this elderly hypertensive patient with baseline dyspnea and edema on antihypertensive and diuretic therapy may serve as plausible alternative explanations for the occurrence of ascites. There was no data provided within the case to suggest the presence of a hepatic disorder as the cause of the ascites.

There were 3 additional cases involving increased hepatic enzymes: **MAG-2009-0000799** (abnormal hepatic function), **DEU-2009-0005381** (hepatic enzymes increased), and **GBR-2009-0005406** (alkaline phosphatase increased, transaminases increased, and gamma-GT increased). All 3 cases involved the use of concomitant medications, which are known to be associated with hepatic abnormalities, or contained alternative explanations for the events. There was also one insufficiently documented case of [unspecified] liver injury received via US litigation sources (**USA-2008-0033084**).

MAH Comment: Increased hepatic enzymes is listed in the Undesirable Effects section in the oxycodone CCDS. All of these cases were confounded by underlying conditions (e.g. metastatic cancer, transfusion history), concomitant drugs known to be associated with hepatic abnormalities (e.g. acetaminophen), contained alternative explanations, or were insufficiently documented preventing a proper assessment. The MAH will continue to monitor serious hepatic events in patients treated with oxycodone. Based on the available information, no change to the oxycodone CCDS is warranted at this time.

9.9.2 Sequelae of Constipation

Cases with event terms of constipation or one of the following PTs received during this reporting period were reviewed: abdominal distention, abdominal pain, abdominal pain upper, abdominal discomfort, abdominal rigidity, anal fissure, colitis, colitis ischemic, faecalith, faecaloma, gastrointestinal hemorrhage, haematochezia, ileus, intestinal obstruction, intestinal prolapse, large intestine perforation, neurogenic bowel, rectal hemorrhage, vomiting projectile, rectal tenesmus, rectal discharge. Thirty one (31) cases were identified; 15 of the 31 cases included the event of constipation. The majority of these cases involved patients with significant underlying disease, advanced age, on multiple concomitant medications who experienced severe cases of constipation or ileus prompting / prolonging hospitalization; with no reported sequelae. The remaining cases are summarized below.

DEU-2009-0005534 involved a female patient with a history of intestinal obstruction while receiving morphine sulphate and chronic pain due to various injuries and fractures of the entire backbone and several big joints from a fall who experienced constipation while receiving oxycodone, refractory to treatment with various laxatives. She had fresh blood with each defecation and demonstrated solidified stool consisting of coproliths, rectocele and cystocele on colonoscopy. Surgery was performed to remove the rectocele and cystocele, therapy with oxycodone was switched to Targin (oxycodone/naloxone), and the patient recovered.

USA-2009-0039977 involved a female patient in her 60's given OxyContin post hip replacement along with a laxative but didn't take it, resulting in acute colonic ischemia and perforation attributed to constipation secondary to postoperative narcotic analgesia. She underwent emergency colectomy, with ileostomy and required further bowel surgery.

USA-2009-0038764 involved an 18-year-old female addicted to OxyContin and methadone who had just returned from a rehabilitation center, experienced severe constipation and straining from opioid use and developed a prolapsed colon.

GBR-2009-0005108 involved a female patient on oxycodone who experienced pseudo-bowel occlusion, abdominal pain, constipation and nausea. The patient was hospitalized.

USA-2008-0039973 involved a 20-year-old female status post discectomy treated with OxyContin 20mg three times daily and OxyNorm, along with a laxative (NOS), who experienced nausea, vomiting, decreased food intake, dehydration, constipation, and inadequate pain relief. After 10 days of therapy with the laxative and an enema, she hadn't had a bowel movement and was admitted overnight.

GBR-2009-0005638 involved a female patient with a history of headache secondary to trauma and opioid-induced constipation. Concomitant medications included Movicol (macrogol 3350). Approximately 8-9-days after initiating OxyContin 50 mg orally twice daily the patient presented with blackish projectile vomiting. She was diagnosed with ileus and aspiration pneumonia secondary to projectile vomiting. OxyContin was stopped and she recovered from the ileus and blackish projectile vomiting. The outcome of the aspiration pneumonia was reported as not recovered.

GBR-2009-0005204 (faecaloma) involved a 91-year-old male taking multiple medications including OxyContin, OxyNorm, and macrogol who experienced somnolence, urinary incontinence, physical disability, urinary retention, and acute renal failure, prompting hospitalization, after the dose of OxyContin was increased to 20 mg bid. The patient presented with confusion, disorientation, bladder distention and faecaloma. The patient was treated for these events and recovered.

GBR-2009-0005394 (perianal fissure) involved a 60-year-old male participating in a Pfizer clinical trial of "blanked drug" or Bevacizumab in combination with paclital and carboplatin as first-line treatment for patients with advanced non-small cell lung cancer. The patient received multiple study and concomitant medications including OxyNorm, oxycodone, and macrogol and microlax enemas for constipation. The patient developed an anal fistula and a manual evacuation was performed. The patient was discharged on diltiazem topical treatment and laxatives. The patient was reported to be recovering from the event at the time of last contact.

MAH Comment: Most of the cases listed above involved patients who required hospitalization for treatment of constipation or ileus. Many of these patients were elderly, on multiple medications, and/or with serious underlying illnesses, all of which may have contributed to the events in these cases. The MAH will continue to monitor serious complications of constipation in patients treated with oxycodone. Constipation and ileus are listed events in the Undesirable Effects section of the

oxycodone CCDS. Based on the available information, no change to the oxycodone CCDS is warranted at this time.

9.9.3 Aggression

There were two serious events of aggression received during this reporting interval.

GBR-2009-0005610 involved a patient enrolled in a non-Company study of patients with metastatic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. The patient received OxyNorm since November 2008. Concomitant drugs included hydromorphone, amitriptyline, methadone, and ethanol. The patient experienced anxiety, agitation, possible psychosis and frequent panic attacks since initiating OxyNorm. In August 2009 the patient became aggressive with increasing anxiety, agitation and confusion and was hospitalized due to mood alterations. A CT scan revealed disease progression with liver metastasis and pleural metastasis. At the time of last contact, the patient's condition was improving.

USA-2009-0040388 involved a male patient taking OxyContin for an unspecified indication who experienced behavior changes and became aggressive with domestic violence after taking the medication. The patient was hospitalized in a behavioral health institution and was put on unspecified antipsychotic medications. No further details provided.

MAH Comment: A cumulative safety analysis was performed to formally investigate the potential association between oxycodone and aggression, and was attached to the December 2008 PSUR. Section 4.8 (Undesirable Effects) of the oxycodone CCDS currently includes agitation, affect lability, confusional state and thinking abnormal. A review of the cases received during this PSUR period does not alter the findings of the safety analysis; a formal relationship between oxycodone and aggression cannot be confirmed. No changes to the oxycodone CCDS are warranted at this time. The MAH will continue to monitor reports of aggression in the next PSUR period and re-assess the association between oxycodone and aggression at that time.

9.9.4 Tooth Disorders

There were 3 cases involving events associated with tooth disorders received during this PSUR period.

USA-2009-0036933 involved a 46-year-old female with Crohn's disease, Barrett's disease, fibromyalgia, Sjogren's syndrome and rheumatoid arthritis. Concomitant medications included venlafaxine, celecoxib, esomeprazole, oxybutynin, rituximab, cevimeline hydrochloride and warfarin. The patient had been taking OxyContin 40mg 5 times daily per day for about two years for pain associated with fibromyalgia. For seven to ten years, the patient took a generic oxycodone and discontinued this two years ago. The patient reported that she experienced dry and raw mouth, two broken teeth, cavities forming at gum line, and rotting teeth. A reporting nurse noted that the patient has a history of attribution of symptoms to medication and noted that she is taking many agents that contribute to dry mouth and associated problems. The nurse practitioner considered the events broken teeth, pulmonary embolism, dry mouth and dry lips to be not related

to OxyContin.

DEU-2009-0005266 involved a 53-year-old male who received treatment with Oxygesic since JAN2008 and lost two "healthy" teeth. Reportedly the patient had not contacted his dentist in this matter yet. The pharmacist found the causal relationship of the adverse event and the treatment with Oxygesic to be not assessable.

DEU-2009-0005509 involved a 55-year-old female with pain due to inoperable spondylolisthesis who was treated with Oxygesic 50mg three times daily for six to seven years and experienced recurrent, poorly treatable infections on the back teeth. Since early 2009 she also experienced varicella zoster infection with facial paralysis on the right.

MAH Comment: A safety analysis of tooth disorders and a benefit risk assessment specific to tooth caries were performed during a previous reporting period and presented in the December 08 PSUR. Based on the review of the available information, Section 4.8 of the oxycodone CCDS was updated to include the preferred term of "dental caries" (frequency: uncommon). The MAH will continue to monitor reports of tooth disorders in patients treated with oxycodone.

9.9.5 Potential Interaction with Proton Pump Inhibitors

There were no reports of potential drug interactions with proton pump inhibitors received during this PSUR period. The Company will continue to monitor potential drug interactions between oxycodone and proton pump inhibitors.

9.9.6 QTc Interval Prolongation

A recently published literature article reported a possible association between higher opioid dosages and a prolonged QTc interval for oxycodone.[2] A Safety Analysis was conducted to review the currently available information regarding a possible association between oxycodone therapy and QTc prolongation and can be found in Appendix IXa.

There were no events received during this reporting period involving the following MedDRA preferred terms (PTs) from the MSSO SMQ for Torsades de Pointes / QT prolongation: electrocardiogram (ECG) QT interval abnormal, electrocardiogram (ECG) QT prolonged, Long QT syndrome congenital, Long QT syndrome, Torsades de Pointes, and ventricular tachycardia. There were 2 insufficiently documented reports involving the PT of arrhythmia received during this reporting interal. GBR-2009-0005639 involved a report of suspected cardiac arrhythmia in a male in his 50's, confounded by a history of tobacco use, excessive alcohol use, and concomitant therapy with a tricyclic antidepressant (discussed above in Section 6.4, Individual case presentation). The remaining case involved a report of a fatal overdose associated with a "cardiac arrhythmia due to drug effect" received via US litigation sources (LEG-2009-0007242).

[2] Fanoe, S et al. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. British Journal of Clinical Pharmacology, 2009;67(2):172-179.

Based on the available information, no changes to the oxycodone CCDS are warranted at this time. The MAH will continue to monitor reports of prolonged QTc interval in patients treated with oxycodone. An external, expert cardiology opinion has been requested by the MAH to review the available data regarding the possible association between oxycodone therapy and QTc prolongation. The expert cardiology statement will be included in the next oxycodone PSUR.

9.9.7 Hypertension

A Safety Analysis and Benefit/Risk Assessment were performed to assess the relationship between the therapeutic use of oxycodone and reports of hypertension and increased blood pressure and can be found in Appendix IXb. Based on the review of the available information, an association between oxycodone therapy and the occurrence of increased blood pressure/ hypertension cannot be formally established. No change to the CCDS for oxycodone is warranted at this time.

The Company will continue routine surveillance activities for reports of hypertension, increased blood pressure in patients treated with oxycodone.

10. CONCLUSION

Overall, the reports received during this PSUR interval are similar in nature to those described in previous PSURs. Consistent with previous PSURs, the majority of reports describe either adverse effects known to be associated with oxycodone and listed in the CCDS, known clinical consequences of listed events, or events without likely causal association with oxycodone but that occur commonly in the patient population taking oxycodone for chronic pain. The information in this PSUR does not indicate any change in the characteristics of listed reactions and the evaluation of the reported events did not reveal any new safety signals.

A large number of reports described events consistent with overdosage and/or oxycodone abuse and addiction, alone or together with other legal and/or illegal substances. These reports typically contain very little clinically evaluable information that might permit the identification of any new or unexpected adverse events possibly attributable to oxycodone. The MAH will continue to closely monitor international safety reports, suspected interactions between oxycodone and other drugs, and cases involving hepatic dysfunction, sequelae of constipation, aggression, tooth disorders, potential interactions with proton pump inhibitors, and prolongation of the QTc interval.

The oxycodone CCDS was revised as of 07August 2009 to include 2 additional preferred terms (cholestasis and dental caries) in Section 4.8 Undesirable Effects, updated text regarding the co-administration of oxycodone with drugs that inhibit or induce CYP2D6 and CYP3A4 pathways in Section 4.5 Drug Interactions, and updated text in the Preclinical Safety Information Section 5.3, as well as various reference changes.

No additional changes to the product safety information are warranted at this point in time based on the information contained in this report, which reaffirms the favorable benefit-risk balance for oxycodone when used in accordance with the instructions given in the CCDS.

11. COMPANY CORE DATA SHEET

The CCDS effective 07August2009 was used as the reference safety information for this PSUR. A copy of this reference is included in Appendix III.

Appendix I – Worldwide Marketing Authorization Status

Appendix I – Worldwide Marketing Authorization Status

NOTES: Entries added during this reporting interval are presented in bold print
See last page of this table for footnotes

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Argentina	OxyContin Tablets 10, 20, 40 mg	07-Aug-97	01-Mar-98	07-Aug-12	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyRapid Capsules 5mg	5-Apr-99	Not Marketed	**05-Apr-14**	Relief of moderate to moderately severe pain
	OxyRapid Capsules 10 & 20 mg	**30-Mar-09**	**Not Marketed**	**30-Mar-14**	**Relief of moderate to moderately severe pain**
Australia	OxyContin Tablets 5 mg	24-Mar-03	01-Nov-03	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyContin Tablets 10, 20, 40, 80 mg	15-Jul-99	06-Sep-99	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyContin Tablets 160 mg	17-May-02	Not marketed	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyNorm Capsules 5, 10, 20 mg	9-Oct-00	**01**-Feb-01	None[1]	The management of opioid responsive, moderate to severe pain
	OxyNorm oral solution 5mg/5ml	13-Nov-01	01-Mar-03	None[1]	The management of opioid responsive, moderate to severe pain
	OxyNorm injection 10 mg/ml (1 and 2 ml)	08-Nov-05	01-Mar-07	None[1]	The management of opioid responsive moderate to severe pain

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin tablets 15, 30 mg	14-Jul-08	**01-Apr-09**	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyContin 60mg	9-Apr-09	Not marketed	None[1]	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.
	OxyContin 120mg	**9-Apr-09**	**Not marketed**	**None[1]**	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.
Austria	OxyContin retard 5 mg Filmtabletten	05-Oct-05	01-Dec-05	None[2]	For the treatment of severe pain.
	OxyContin retard 10, 20, 40 & 80 mg Filmtabletten	26-Nov-99	01-Apr-01	None[2]	For the treatment of severe pain.
	OxyNorm 5, 10 & 20 mg -Kapseln	23-Dec-04	01-Apr-05	**Renewal pending**	For the treatment of severe pain.
	OxyNorm 10 mg/ml injektionslösung	03-Feb-09	**01-Jun-09**	14-Dec-11	For the treatment of severe pain.
Belgium	OxyContin 5 mg	29-Aug-05	04-Dec-06	None[2]	Severe to most severe pain.
	OxyContin 10, 20, 40 & 80 mg	30-Jun-03	17-Nov-03	None[2]	Severe to most severe pain.
	OxyNorm Instant 5, 10 & 20 mg orodispergeerbare tabletten	22-Jul-08	Not marketed	21-Dec-12	Severe to most severe pain.
	OxyContin 10 mg/ml, oplossing voor injectie (1 ml & 2 ml)	**21-Apr-09**	**Not marketed**	**09-Jan 12**	**Severe to most severe pain.**

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin 50 mg/ml, oplossing voor injectie	**04-Sep-09**	**Not marketed**	**29-May-14**	**Severe to most severe pain.**
	OxyContin 15, 30, 60, 120 & 160 mg	**07-Oct-09**	**Not marketed**	**06-Nov-13**	**Severe to most severe pain.**
Bolivia	OxyContin Tablets 10 mg	27-Jan-98	01-Jul-99	27-Jul-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin Tablets 20 mg & 40 mg	27-Jan-98	01-Jul-99	22-Jul-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyRapid Capsules 5 mg	24-May-00	Not marketed	10-Aug-13	Relief of moderate to moderately severe pain
Bosnia	OxyContin 10, 20 & 40 mg	22-Dec-08	Not marketed	22-Dec-13	Moderate to severe pain.
Brazil	OxyContin Tablets 10, 20, 40 mg	18-Aug-99	1-Mar-00	**Renewal pending**	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Bulgaria	OxyContin modified-release tablets 10, 20, 40 & 80 mg	03-Jan-01	01-Dec-04	13-Jun-11	For the treatment of moderate and severe pain.
Canada	OxyContin Tablets 5 mg	23-Sept-04	01-Apr-05	None[1]	Moderate to severe pain, requiring continuous use of an opioid analgesic preparation for several days or more.
	OxyContin Tablets 10, 20, 40, 80 mg	04-Jan-96	04-Jun-96	None[1]	Moderate to severe pain, requiring continuous use of an opioid analgesic preparation for several days or more.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin Tablets 120 mg	04-Mar-09	Not marketed	None[1]	Moderate to severe pain, requiring continuous use of an opioid analgesic preparation for several days or more.
	OxyContin Tablets 160 mg	16-Dec-02	Not marketed	None[1]	Moderate to severe pain, requiring continuous use of an opioid analgesic preparation for several days or more.
	OxyContin Tablets 15, 30 and 60 mg	04-Mar-09	**01-May-09**	None[1]	Moderate to severe pain, requiring continuous use of an opioid analgesic preparation for several days or more.
	Oxy·IR Tablets 5 mg	01-Aug-97	31-Mar-00	None[1]	Relief of moderate to severe pain.
	Oxy·IR Tablets 10, 20 mg	18-May-99	31-Mar-00	None[1]	Relief of moderate to severe pain.
Chile	OxyContin 10 mg Modified-release Tablets	19-May-98	01 Jul-99	19-May-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin 20, 40 mg Modified-release Tablets	30-Apr-98	01 Jul-99	30-Apr-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyRapid Capsules 5 mg	05-Dec-00	Not marketed	04-Dec-10	Relief of moderate to moderately severe pain
China	OxyContin Tablets 5, 10, 20, 40 mg	21-Jan-2004 Import Registration Licence	17-Sept-04	**26-May-14**	For relief of moderate to severe pain of prolonged duration
Colombia	OxyContin Tablets 10, 20, 40 mg	02-Apr-98	24-Oct-00	27-Oct-18	Narcotic analgesic

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Costa Rica	OxyContin Tablets 10, 20, 40 mg	12-Nov-08	Not Marketed	12-Nov-13	Moderate to severe pain where use of an opioid Analgesic is appropriate for more than a few days
Croatia	OxyContin 10, 20, 40 & 80 mg (56 tablet packs)	14-Feb-05	18-Mar-06	14-Feb-10	For the treatment of severe pain.
	OxyContin 10, 20, 40 & 80 mg (30 and 60 tablet packs)	04-Oct-06	Not marketed	04-Oct-11	For the treatment of severe pain.
Cyprus	OxyContin 10, 20, 40 & 80 mg film-coated, prolonged-release tablets	10-Feb-00	27-Feb-06	09-Feb-10	For treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyContin 5 mg film-coated, prolonged-release tablet	29-May-08	Not marketed	28-May-13	For treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyNorm 5,10 & 20 mg	27-Mar-08	13-Oct-08	26-Mar-13	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyNorm Solution for Injection or Infusion 10mg/ml	31-Mar-08	13-Oct-08	30-Mar-13	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Czech Republic	OxyContin tablets 10, 20, 40 & 80 mg	26-Apr-00	01-Apr-01	01-Jun-10	Moderate to severe pain.
Denmark	OxyContin tablets 5 mg	06-Jan-04	19-Jan-04	None[2]	Moderate to severe long term pain which does not respond to non-opioid analgesics
	OxyContin tablets 10, 20 & 40 mg	05-Sep-96	01-Dec-96	None[2]	Moderate to severe long term pain which does not respond to non-opioid analgesics
	OxyContin tablets 80 mg	17-Sep-98	22-Feb-99	None[2]	Moderate to severe long term pain which does not respond to non-opioid analgesics
	OxyContin tablets 160 mg	04-Jul-02	Not marketed	None[2]	Moderate to severe long term pain which does not respond to non-opioid analgesics
	OxyNorm capsules 5, 10 & 20 mg	24-Jul-01	24-Dec-01	None[2]	Moderate to severe pain which does not respond to non-opioid analgesics
	OxyNorm oral solution 1mg/ml, & 10mg/ml	18-May-01	12-Dec-01	None[2]	Moderate to severe pain which does not respond to non-opioid analgesics
	OxyNorm solution for injection and infusion 10 mg/ml	03-Oct-03	Mar-04	None[2]	Moderate to severe pain which does not respond to non-opioid analgesics
Dominican Republic	OxyContin Tablets 10, 20 & 40 mg	13-Feb-04	01-Feb-98	Renewal Pending	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Ecuador	OxyContin Tablets 10, 20 & 40 mg	29-Jun-98	01-Jun-99	11-Aug-14	Moderate to severe pain where use of an opioid is appropriate for more than a few days

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
El Salvador	OxyContin Tablets 10, 40 mg	8-Apr-02	Sept-07	15-Aug-11	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin 20 mg Tablets	8-Apr-02	Sep-07	24-Aug-12	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Estonia	OxyContin 10, 20, 40 & 80 mg toimeainet prolongeeritult vabastavad tabletid	25-Feb-00	15-Mar-01	17-Jun-10	For the treatment of moderate and severe pain.
Finland	OxyContin tablets 5 mg	21-Jan-02	Feb-04	02-Oct-10	Moderate to severe pain.
	OxyContin tablets 10, 20 & 40 mg	08-Jan-96	23-Sep-96	None[2]	Moderate to severe pain.
	OxyContin tablets 15 & 30 mg	12-Mar-08	Not marketed	12-Mar-12	Moderate to severe pain.
	OxyContin tablets 60 & 120 mg	23-Apr-08	Not marketed	23-Apr-13	Moderate to severe pain.
	OxyContin tablets 80 mg	12-Oct-98	01-Sep-99	None[2]	Moderate to severe pain.
	OxyContin tablets 160 mg	21-Jan-02	Not marketed	02-Oct-10	Moderate to severe pain.
	OxyNorm capsules 5, 10 & 20 mg	15-Jan-01	12-Dec-01	02-Oct-10	Moderate to severe pain.
	OxyNorm liquid 1 mg/ml & concentrate 10 mg/ml	02-Oct-00	26-Nov-01	02-Oct-10	Moderate to severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyNorm 10 mg/ml solution for injection and infusion	21-Apr-04	Nov-04	02-Oct-10	Moderate to severe pain.
	OxyNorm orodispersible tablets 5 mg, 10 mg & 20 mg	26-Feb-08	Not marketed	26-Feb-13	Moderate to severe pain.
	OxyNorm 50 mg/ml solution for injection/infusion	07-Oct-08	Not marketed	07-Oct-13	Moderate to severe pain.
France	OxyContin L.P. 5 mg **prolonged release tablets**	14-Mar-05	11-Sep-06	14-Mar-10	Chronic pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).
	OxyContin L.P. **10, 20, 40 & 80 mg prolonged release tablets**	11-Jul-00	02-Apr-02	11-Jul-10	Chronic pain due to cancer, severe or unresponsive to weaker analgesics, in adults (above 18 years of age).
	OxyContin L.P. 15, 30, 60 & 160 mg **prolonged release tablets**	11-Mar-08	Not marketed	11-Mar-13	Chronic pain due to cancer, severe or unresponsive to weaker analgesics, in adults (above 18 years of age).
	OxyContin L.P. 120 mg **prolonged release tablets**	11-Mar-08	16-Sep-09	11-Mar-13	Chronic pain due to cancer, severe or unresponsive to weaker analgesics, in adults (above 18 years of age).
	OxyNorm capsules 5, 10 & 20 mg	11-Jun-03	01-Jul-04	**None**[2]	Pain due to cancer, severe or unresponsive to weaker analgesics, in adults (above 18 years of age).
	OxyNorm 10mg/ml oral solution	22-Mar-05	Not marketed	22-Mar-10	Pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyNorm 10mg/ml **solution for injection**	16-Mar-05	27-Aug-07	16-Mar-10	Chronic pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).
	OxyNorm ORO orodispersible tablets 5 & 10 mg	19-Jul-07	**05-Oct-09**	19-Jul-12	Pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).
	OxyNorm ORO orodispersible tablets 20 mg	16-Jul-07	**05-Oct-09**	16-Jul-12	Pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).
	OxyNorm 50 mg/ml solution for injection	19-Aug-08	**23-Feb-09**	19-Aug-13	Chronic pain due to cancer, severe or unresponsive to weaker analgesics in adults (above 18 years of age).

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Germany	OXYGESIC 5 mg	07-Oct-04	01-Dec-04	None[2]	Severe to most severe pain.
	OXYGESIC 10, 20 & 40 mg	15-May-08	01-Aug-98	None[2]	Severe to most severe pain.
	OXYGESIC 80 mg	06-Feb-01	01-Mar-01	None[2]	Severe to most severe pain.
	OxyContin 5 mg	07-Oct-04	Not marketed	08-Nov-12	Moderate to severe pain.
	OxyContin 10, 20, 40 & 80 mg	19-May-03	Not marketed	08-Nov-12	Moderate to severe pain.
	OXYGESIC injekt 10 mg/1 ml & 20 mg/2 ml	**05**-Jan-07	01-Jul-07	09-Jan-12	Severe to most severe pain.
	OxyNorm Injektionslösung 10 mg & 20 mg	**05**-Jan-07	Not marketed	09-Jan-12	Severe to most severe pain.
	Oxygesic akut 5, 10 & 20 mg	**22-May-07**	01-Oct-07	24-May-12	Severe to most severe pain.
	Oxygesic Lösung 1mg/ml	**21-May-07**	Not marketed	**23-May-12**	Severe to most severe pain.
	Oxygesic Lösung 10mg/ml	**21-May-07**	Not marketed	**23-May-12**	Severe to most severe pain.
	OxyNorm Kapseln 5, 10 & 20 mg	**22-May-07**	Not marketed	**24-May-12**	Severe to most severe pain.
	OxyNorm Lösung 1mg/ml	**21-May-07**	Not marketed	23-May-12	Severe to most severe pain.
	OxyNorm Lösung 10mg/ml	**21-May-07**	Not marketed	23-May-12	Severe to most severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	Oxygesic Dispersa 5, 10 & 20 mg	**26-May-09**	**Not marketed**	**21-Dec-12**	**Severe to most severe pain.**
Greece	OxyContin 10, 20, 40 & 80 mg	21-Oct-03	Not marketed	None[2]	Severe to most severe pain.
Guatemala	OxyContin Tablets 10 mg	05-May-99	05-Oct-00	25-Aug-**14**	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin Tablets 20 mg & 40 mg	05-May-99	05-Oct-00	21-Oct-**14**	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Honduras	OxyContin 10, & 40 mg	18-Oct-06	July-07	18-Oct-11	Moderate to severe pain where use of an opioid is appropriate for more than a few days.
	OxyContin 20 mg	11-Oct-06	July-07	11-Oct-11	Moderate to severe pain where use of an opioid is appropriate for more than a few days.
Hungary	OxyContin 10, 20, 40 & 80 mg retard filmtabletta	30-Nov-99	01-Dec-00	31-Dec-09	For the treatment of severe pain.
Iceland	OxyContin 5 mg	19-Aug-05	Dec-05	None[2]	Severe to most severe pain.
	OxyContin 10, 20, 40 & 80 mg	24-Jan-03	May-03	None[2]	Severe to most severe pain.
	OxyNorm Dispersa 5, 10 & 20 mg	25-Feb-09	Not marketed	21-Dec-12	Severe to most severe pain
	OxyNorm 10mg/ml solution for injection	14-Jan-09	Not marketed	09-Jan-12	Moderate to severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Israel	OxyContin Tablets 5 mg	28-Oct-04	Sep-05	**Renewal in Process**	Moderate to severe chronic pain
	OxyContin Tablets 10 & 20 mg	01-Apr-96	01-Dec-96	31-Mar-11	Moderate to severe chronic pain
	OxyContin Tablets 40 &80 mg	01-Feb-98	01-Jan-99	31-Jan-13	Moderate to severe chronic pain
Italy	OxyContin 5 mg tablets	19-Jun-07	20-Aug-07	None[2]	For the treatment of severe pain.
	OxyContin 10, 20, 40 & 80 mg tablets	03-Apr-00	21-Mar-05	None[2]	For the treatment of severe pain.
Japan	OxyContin 5, 10, 20 & 40 mg Tablets	16-Apr-03	07-Jul-03	None[1]	Analgesic for various cancers accompanied with moderate to severe pain
	OxiNorm powder 0.5%	20-Oct-06	05-Feb-07	None[1]	Analgesic for various cancers accompanied with moderate to severe pain
Korea	OxyContin 10, 20 & 40 mg Tablets	01-Sep-00	13-Mar-01	None[1]	Moderate to severe pain where use of an opioid Analgesic is appropriate
	OxyContin 80mg Tablets	31-Mar-09	Not marketed	None[1]	Moderate to severe pain where use of an opioid Analgesic is appropriate
	IR Codon tablet 5mg	15-Oct-01	Jun-04	None[1]	Moderate to severe pain where use of an opioid Analgesic is appropriate
	OxyNorm injection 10mg/ml	31-Mar-09	Not marketed	None[1]	Moderate to severe acute pain where use of an opioid Analgesic is appropriate
Latvia	OxyContin tablets 10, 20, 40 & 80 mg	08-Jul-02	01-May-03	None[2]	Severe to most severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Luxembourg	OxyContin 5 mg	27-Oct-05	04-Dec-06	None[2]	Severe to most severe pain.
	OxyContin 10, 20, 40 & 80 mg	30-Sep-03	17-Nov-03	None[2]	Severe to most severe pain.
	OxyNorm Instant 5, 10 & 20 mg	12-Nov-08	Not marketed	21-Dec-12	Severe to most severe pain.
	OxyContin 10 mg/ml oplossing voor injectie	**10-Aug-09**	**Not marketed**	**09-Jan-12**	**Severe to most severe pain.**
Malaysia	OxyContin Tablets 10, 20, 40 & 80 mg	23-Aug-01	25-Sep-05	23-Aug-11	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
Mexico	OxyContin Tablets 10, 20 & 40 mg	29-Aug-97	Not marketed	03-Oct-13	Narcotic analgesic/moderate to severe pain where use of an opioid is appropriate for more than a few days
Netherlands	OxyContin tablets 5 mg	15-Jul-02	Sep-02	None[1]	For the treatment of severe chronic pain which requires the use of strong opioids.
	OxyContin tablets 10, 20, 40 & 80 mg	10-Apr-00	Dec-00	None[1]	For the treatment of severe chronic pain which requires the use of strong opioids.
	OxyNorm capsules 5, 10 & 20 mg	09-Dec-02	01-Feb-03	None[1]	For the treatment of severe pain which requires the use of strong opioids.
	OxyNorm drank 1 mg/ml & 10 mg/ml	09-Apr-03	01-Nov-03	None[1]	For the treatment of severe pain which requires the use of strong opioids.
	OxyNorm Injection 10 mg/ml	16-Feb-04	01-Mar-04	None[1]	For the treatment of severe pain which requires the use of strong opioids and for the treatment of severe postoperative pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
New Zealand	OxyContin Tablets 5 mg	14-Jun-05	01-Aug-05	None[1]	For the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyContin Tablets 10, 20, 40 & 80 mg	08-Feb-01	01-Aug-05 (relaunched)	None[1]	For the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyContin Tablets 15 & 30 mg	**09-Jul-09**	**Not marketed**	**None**	**For the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia**
	OxyNorm Capsules 5, 10 & 20 mg	08-Feb-01	1-Jan-05	None[1]	For the treatment of opioid responsive moderate to severe pain
	OxyNorm oral solution 5mg/5ml	23-Mar-06	1-Apr-07	None[1]	The management of opioid responsive, moderate to severe pain
	OxyNorm injection 10 mg/ml	17 Aug 06	1-Apr-07	None[1]	The management of opioid responsive, moderate to severe pain
Nicaragua	OxyContin Tablets 10, 20 & 40 mg	12-Aug-02	Nov-07	11-Aug-12	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Norway	OxyContin tablets 5 mg	26-Jun-03	15-Sep-03	**None[2]**	For the treatment of severe pain.
	OxyContin tablets 10, 20 & 40 mg	31-Oct-00	10-Apr-01	31-Oct-10	For the treatment of severe pain.
	OxyContin tablets 80 mg	29-Aug-01	01-Nov-01	31-Oct-10	For the treatment of severe pain.
	OxyNorm capsules 5, 10 & 20 mg	17-Apr-02	01-May-02	None[2]	For the treatment of severe pain.
	OxyNorm oral solution 1 mg/ml & 10mg/ml	17-Apr-02	01-Oct-02	None[2]	For the treatment of severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyNorm 10 mg/ml solution for injection and infusion	16-Dec-04	01-Jun-05	16-Dec-09	Severe pain.
	OxyNorm orodispersible tablets 5, 10 & 20 mg	13-Jun-08	Not marketed	13-Jun-13	Severe pain.
Panama	OxyContin 10 & 40mg tablets	10-Mar-09	Not Marketed	10-Mar-14	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin 20mg tablets	**15-Jul-09**	**Not Marketed**	**15-Jul-15**	**Moderate to severe pain where use of an opioid is appropriate for more than a few days**
Paraguay	OxyContin Tablets 10 & 20 mg	16-Oct-98	01-Mar-00	Renewal pending	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin Tablets 40 mg	16-Oct-98	01-Mar-00	21-Feb-10	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	Oxy **Rapid** Capsules **5 mg**	**26-Jul-00**	**Not marketed**	**21-Feb-11**	**Relief of moderate to moderately severe pain**
Peru	OxyContin Tablets 10 mg	10-Oct-97	01-Oct-98	04-Apr-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days
	OxyContin Tablets 20 mg	10-Oct-97	01-Oct-98	04-Mar-13	Moderate to severe pain where use of an opioid is appropriate for more than a few days

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin Tablets 40 mg	10-Oct-97	01-Oct-98	24-Nov-12	Moderate to severe pain where use of an opioid is appropriate for more than a few days
Philippines	OxyContin Tablets 5 mg	28-Dec-05	Aug-06	28-Dec-11	For the management of moderate to severe pain
	OxyContin Tablets 10, 20, 40, 80 mg	09-Aug-02	Sep-02	09-Aug-11	For the treatment of moderate to severe pain in patients with cancer and post-operative pain
	OxyNorm Capsules 5 mg and 10 mg	20-Jul-06	Aug-06	20-Jul-11	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of strong opioid.
	OxyNorm Capsules 20 mg	20-Jul-06	Not marketed	**Renewal in process**	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of strong opioid.
	OxyNorm Injection 10mg/mL	**31-Jul-09**	**Not marketed**	**31-Jul-12**	**For the treatment of moderate to severe pain in patients with cancer and post-operative pain; for the treatment of sever pain requiring the use of strong opioids.**
Poland	OxyContin 10, 20, 40 & 80 mg	26-Mar-08	26-Jun-08	08-Nov-12	Moderate to severe pain.
	OxyContin 5 mg	26-Mar-08	30-Sep-08	08-Nov-12	Moderate to severe pain.
	OxyContin solution for injection and infusion	18-Mar-09	Not marketed	09-Jan-12	Moderate to severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Portugal	OxyContin 5 mg comprimidos de libertação prolongada	28-Oct-05	Not marketed	None[2]	Severe to most severe pain.
	OxyContin 10, 20, 40 & 80 mg comprimidos de libertação prolongada	09-May-03	Not marketed	None[2]	Severe to most severe pain.
	OxyNorm ORO 5, 10 & 20 mg Comprimidos orodispersíveis	28-May-08	Not marketed	28-May-13	Severe to most severe pain.
	Oxycontin 10 mg/ml Solução injectável	31-Mar-09	Not marketed	09-Jan-12	Moderate to severe pain.
Republic of Ireland	OxyContin prolonged release tablets 5 mg	22-Nov-02	14-Apr-03	None[2]	For the treatment of severe pain.
	OxyContin prolonged release tablets 10, 20, 40 & 80 mg	28-May-98	01-Jan-99	None[2]	For the treatment of severe pain.
	OxyNorm capsules 5, 10 & 20 mg	28-Apr-00	01-Sep-00	27-Apr-10	For the treatment of severe pain.
	OxyNorm liquid 1 mg/ml oral solution	**24-Apr-00**	Not marketed	27-Apr-10	For the treatment of severe pain.
	OxyNorm concentrate 10 mg/ml oral solution	28-Apr-00	01-Nov-00	27-Apr-10	For the treatment of severe pain.
	OxyNorm 10 mg/ml solution for injection or infusion	15-Dec-06	02-Apr-07	14-Dec-11	For the treatment of severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
Romania	OxyContin 10 mg film-coated tablets	14-Oct-03	Jun-05	Renewal pending	Treatment of moderate to extreme pain.
	OxyContin 20, 40 & 80 mg film-coated tablets	29-Aug-03	Jun-05	Renewal pending	Treatment of moderate to extreme pain.
Singapore	OxyContin 5, 10, 20, 40 & 80 mg Tablets	07-Apr-05	30-Sep-05	06-Apr-10	The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia
	OxyNorm 5, 10, & 20 mg Capsules	07-Apr-05	30-Sep-05	06-Apr-10	The management of opioid responsive, moderate to severe pain.
Slovak Republic	OxyContin 10, 20, 40 & 80 mg prolonged release tablets	29-Jan-01	01-Oct-02	None[2]	For the treatment of moderate to severe pain.
Slovenia	OxyContin 10, 20, 40 & 80 mg filmsko obložene tablete s podaljšanim sproščanjem (blister of 4x14 tablets and 2x14 tablets)	12-Dec-01	01-Aug-03	12-Dec-11	For the relief of moderate to severe pain in patients with cancer and post-operative pain. For the relief of severe pain requiring the use of a strong opioid.
	OxyContin 10, 20, 40 & 80 mg filmsko obložene tablete s podaljšanim sproščanjem (blister of 3x10 tablets and 6x10 tablets)	10-May-05	Not marketed	12-Dec-11	For the relief of moderate to severe pain in patients with cancer and post-operative pain. For the relief of severe pain requiring the use of a strong opioid.
Spain	OxyContin tablets 5mg	22-Mar-07	15-Jan-08	None[2]	Treatment of severe pain.
	OxyContin tablets 10, 20, 40 & 80 mg	21-Nov-00	Jun-04	None[2]	Treatment of severe pain.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyNorm capsules 5, 10 & 20 mg	24-Feb-05	01-Sep-05	27-Apr-10	Treatment of severe pain.
	OxyNorm liquid 1 mg/ml oral solution	28-Feb-05	Not marketed	27-Apr-10	Treatment of severe pain.
	OxyNorm concentrate 10 mg/ml oral solution	18-Feb-05	01-Jan-06	27-Apr-10	Treatment of severe pain.
Sweden	OxyContin tablets 5 mg	21-Mar-03	Jun-03	Renewal pending	Long-term severe opioid sensitive pain such as cancer pain.
	OxyContin tablets 10, 20 & 40 mg	29-Dec-98	01-Jul-99	Renewal pending	Long-term severe opioid sensitive pain such as cancer pain.
	OxyContin tablets 80 mg	15-Dec-00	09-May-01	Renewal pending	Long-term severe opioid sensitive pain such as cancer pain.
	OxyNorm capsules 5, 10 & 20 mg	01-Jun-01	01-Oct-01	Renewal pending	Severe opioid sensitive pain such as cancer pain.
	OxyContin tablets 160 mg	29-Apr-03	Not marketed	Renewal pending	Long-term severe opioid sensitive pain such as cancer pain.
	OxyNorm oral solution 1 mg/ml & 10mg/ml	09-Mar-01	01-Oct-01	Renewal pending	Severe opioid sensitive pain such as cancer pain.
	OxyNorm 10 mg/ml, solution for injection	14-Nov-03	Jun-04	Renewal pending	Severe opioid sensitive pain such as cancer pain.
Switzerland	OxyContin tablets 5 mg	03-Feb-05	01-Jul-05	14-Oct-**14**	Moderate to severe prolonged pain or insufficient effect of non-opioid analgesics.
	OxyContin tablets 10 & 20 mg	24-Jun-99	15-Feb-01	14-Oct-**14**	Moderate to severe prolonged pain or insufficient effect of non-opioid analgesics.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin tablets 40 & 80 mg	24-Jun-99	01-Oct-02	14-Oct-**14**	Moderate to severe prolonged pain or insufficient effect of non-opioid analgesics.
	OxyNorm drops 10 mg/ml	03-Oct-03	01-Feb-04	02-Oct-13	Moderate to severe pain or insufficient effect of non-opioid analgesics.
United Kingdom	OxyContin 5 mg film-coated, prolonged release tablets	21-May-02	10-Jun-02	None[2]	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyContin 10, 20, 40 & 80 mg film-coated, prolonged release tablets	05-Mar-99	27-Jan-00	None[2]	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyNorm capsules 5, 10 & 20 mg	26-Oct-99	14-Jan-00	None[2]	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyNorm liquid 5 mg/5 ml & OxyNorm concentrate 10mg/ml	09-Dec-99	17-Jan-00	None[2]	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyNorm 10 mg/ml solution for injection or infusion	14-Apr-03	12-May-03	None[2]	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	OxyNorm 50 mg/ml solution for injection or infusion	14-Jan-09	**06-Jul-09**	13-Jan-14	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
	Longtec prolonged release tablets 5, 10, 20, 40 & 80 mg	15-Feb-08	Not marketed	**14**-Feb-13	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.
Uruguay	OxyContin 10, 20 & 40 mg Controlled-release Tablets	23-Nov-99	Not marketed	**Renewal Pending**	Moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time
USA	OxyContin 10, 20 & 40 mg Controlled-release Tablets	12-Dec-95	18-Dec-95	None[1]	Moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time
	OxyContin 15, 30 & 60 mg Controlled-release Tablets	18-Sept-06	Jan-08	None[1]	Moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time

Country	Authorised Product Name	Approval Date	Launch Date	Renewal Date	Authorised Indication
	OxyContin 80 mg Controlled-release Tablets	09-Dec-96	01-Jan-97	None[1]	Moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time
	OxyContin 160 mg Controlled-release Tablets	15-Mar-00	20-Apr-00	Not Marketed	Moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time
	OxyIR Immediate-release Capsules 5 mg	N/A	01-Feb-96	None[1]	Relief of moderate to moderately severe pain
Venezuela	OxyContin Tablets 10, 20, & 40 mg	02-Oct-01	01-Nov-96	Renewal pending	Moderate to severe pain where use of an opioid is appropriate for more than a few days.
	OxyRapid Capsules	07-Sep-99	Not Marketed	24-Nov-10	Relief of moderate to moderately severe pain

[1] **No renewal process**
[2] **No further renewals required according to national implementation of Directive 2004/27/EC**

Appendix II – Update of regulatory authority or MAH actions taken for safety reasons

NONE

Appendix III – Company Core Data Sheet (CCDS)
Dated 07 August 2009

COMPANY CORE DATA SHEET

OXYCODONE HYDROCHLORIDE

This Company Core Data Sheet is a summary of relevant core information on this/these product/s. It should be used when Summary of Product Characteristics or other Product Documents are being prepared, or when information regarding this product is being updated. However, details in some sections (indications, dosage, etc.) may differ from country to country, and each national product information document should always be kept in line with the marketing authorization granted by the local regulatory authority. In addition, under the Pharmaceutical Properties section, details of pharmaceutical features should be checked against the pharmaceutical section of the registration file. The Company Core Safety Information is located in Sections 4.3 to 4.9.

Country Responsible

United States of America

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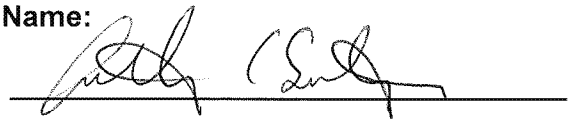
Name: 

Date: 8/12/09

1. NAME OF THE MEDICINAL PRODUCT

Trademark
Please refer to local labeling.

Generic (INN) Name
Oxycodone Hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Please refer to local labeling.

3. PHARMACEUTICAL FORM

Please refer to local labeling.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indication

Pain requiring the use of an opioid analgesic.
Please refer to local labeling.

4.2. Posology and Method of Administration

4.2.1. General

Controlled-release (prolonged-release, extended-release) tablets:
Please refer to local labeling.

Immediate release tablets, capsules and oral liquids:
Please refer to local labeling.

Parenteral
Please refer to local labeling.

4.3. Contraindications

Oxycodone is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated: severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, or paralytic ileus[1]

4.4. Special Warnings and Precautions for Use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly or infirm; patients with severely impaired pulmonary, hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.[2]

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control.[3] Prolonged use of this product [preparation] may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.[4]

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone.[5, 6, 7, 8, 9, 10, 11] [Drug product] should be used with particular care in patients with a history of alcohol and drug abuse.

The controlled release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).[12]

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

For controlled release products:

> [Drug product] is not recommended for pre-operative use or within the first 12-24 hours post-operatively.[13]

For normal / immediate release products (oral):

> [Drug product] should be used with caution pre-operatively and within the first 12-24 hours post-operatively.[13]

For normal / immediate release products (parenteral):

> [Drug product] should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.[13]

4.5. Drug Interactions

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as alcohol, other opioids, sedatives, hypnotics, anti-depressants, sleeping aids, phenothiazines and neuroleptic drugs, etc.[1]

Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone concentrations.[14, 15] Oxycodone doses may need to be adjusted accordingly.

4.6. Pregnancy and Lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.[16][17]

The drug penetrates the placenta and can be found in breast milk[17]

4.7. Effects on Ability to Drive and Use Machines

Oxycodone may impair the ability to drive and use machines.

4.8. Undesirable Effects

The adverse experiences listed below are classified by body system according to their incidence (common or uncommon). Common adverse drug experiences have an incidence of ≥ 1% and uncommon adverse drug experiences have an incidence of < 1%.[18]

Cardiac Disorders	
Uncommon	palpitations (in the context of withdrawal syndrome)[19, 20]
Ear and Labyrinth Disorders	
Uncommon	vertigo[21]
Eye Disorders	
Uncommon	miosis[22] vision abnormal[23]
Gastrointestinal Disorders	
Common	abdominal pain[24] constipation[25] diarrhea[26] dry mouth[27] dyspepsia[28] nausea[29] vomiting[30]
Uncommon	dental caries[31] dysphagia[32] eructation[33] flatulence[34] gastrointestinal disorder[35] ileus[36]
General Disorders and Administration Site Conditions	
Common	asthenic conditions[37] chills[38]
Uncommon	drug tolerance[39] drug withdrawal syndrome[40] edema[41] edema peripheral[42]

malaise[43]
thirst[44]

Hepatobiliary Disorders
Uncommon
cholestasis[45]
increased hepatic enzymes[46]

Immune System Disorders
Uncommon
anaphylactic reaction[47]
anaphylactoid reaction[48]
hypersensitivity[49, 50]

Metabolic and Nutritional Disorders
Common
anorexia[51]

Uncommon
dehydration[52, 53]

Nervous System Disorders
Common
dizziness[54]
headache[55]
somnolence[56]

Uncommon
amnesia[57, 58]
convulsion[59, 60]
hypertonia[61, 62]
hypoaesthesia[63]
muscle contractions involuntary[64]
paresthesia[65, 66]
speech disorder[67]
syncope[68, 69]
taste perversion[70, 71]
tremor[72]

Psychiatric Disorders
Common
anxiety[73]
confusional state[74]
insomnia[75]
nervousness[76]
thinking abnormal[77]

Uncommon
affect lability[78, 79]
agitation[80]
depression[81, 82]
drug dependence[83]
euphoria[84]
hallucinations[85]
libido decreased[86]

Renal and Urinary Disorders
Uncommon
urinary retention[87]

Reproductive System and Breast Disorders	
Uncommon	amenorrhea[88] erectile dysfunction[89]
Respiratory, Thoracic and Mediastinal Disorders	
Common	dyspnea[90, 91]
Uncommon	respiratory depression[2]
Skin and Subcutaneous Tissue Disorders	
Common	hyperhydrosis[92] pruritus[93] rash[94]
Uncommon	dry skin[95, 96] urticaria[97, 98, 99]
Vascular Disorders	
Uncommon	hypotension[100] orthostatic hypotension[101] vasodilation[102]

4.9. Overdosage

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, miotic pupils, bradycardia, hypotension, and death.

A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed[1]

5. PHARMACOLOGICAL INFORMATION

5.1. Pharmacological Properties

Oxycodone HCl is an opioid agonist with no antagonistic action. Its effects are similar to those of morphine[1]

The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity[1]

Endocrine System
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.[103]

Other Pharmacologic Effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.[104]

5.2. Pharmacokinetic Properties

Oxycodone controlled-release tablets release oxycodone more slowly than immediate-release oxycodone tablets or capsules. Release in vitro is pH-independent.[105]

Absorption
The controlled-release tablets exhibit a two-phase absorption pattern with apparent absorption half-times of 0.6 and 6.9 hours. Peak plasma concentration is attained after three hours. The plasma elimination half-life is approximately 4.5 hours.[106] Food intake has little or no effect on the absorption of oxycodone from controlled-release tablets.[106, 107]

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.[108] Oxycodone is metabolized in the liver to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. CYP3A4 and CYP2D6 are the primary enzymes responsible for the formation of noroxycodone, oxymorphone and noroxymorphone. The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes resulted in no significant inhibition of CYP2D6 and CYP3A4 activities, which suggest that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4.[109] Noroxymorphone has been shown to bind to μ-opioid receptor.[110] Although oxymorphone has been shown to be active, the analgesic effects of the metabolites are thought to be clinically insignificant.[15]

The active drug and its metabolites are excreted in both urine and feces.[1] The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.[106]

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.[106]

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.[111]

When compared to normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.[112]

5.3. Preclinical Safety Information

5.3.1. Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence

of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥2 mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioral and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study. [113, 114, 115, 116]

5.3.2. Carcinogenicity

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

5.3.3. Mutagenicity

The results of in vitro and in vivo studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an in vivo micronucleus assay in the mouse. Oxycodone produced a positive response in the in vitro mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two in vitro chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at 48 hours after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point. [117, 118, 119, 120, 121, 122]

6. PHARMACEUTICAL INFORMATION

6.1. Constituents

Please refer to local labeling.

6.2. Incompatibilities

Parenteral Dosage Form

Please refer to local labeling.

6.3. Shelf Life

Please refer to local labeling.

6.4. Special Storage Conditions

Please refer to local labeling.

6.5. Packaging

Please refer to local labeling.

6.6. Instructions for use/handling

Please refer to local labeling.

7. NAME OR STYLE AND PERMANENT ADDRESS OR REGISTERED PLACE OF BUSINESS OF THE HOLDER OF THE MARKETING AUTHORIZATION

Please refer to local labeling.

8. MARKETING AUTHORIZATION NUMBERS

Please refer to local labeling.

9. DATE OF APPROVAL/REVISION

Please refer to local labeling.

10. DATE OF THE CCDS

07 August 2009

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[20] Term: palpitations. Study No. OC91-0402B: Patient No. 04027; OC92-1102: Patient No. 02027

[21] Term: vertigo. Study No. OC91-0402A: Patient No. 08011

[22] Internal White Paper on Miosis, 12-Mar-2003

[23] Term: vision abnormalities. Study No. OC91-0402A: Patient No. 08011; OC91-0907B: Patient No. 07002, 021

[24] Term: abdominal pain. Study No. OC91-0402A: Patient No. 15008, 08016, 12001; OC91-0402B: Patient No. 07014, 04001, 03014; OC91-0907B: Patient No. 15005

[25] Term: constipation. Study No. OC91-0402A: Patient No. 11006, 17027, 08007, 08008; OC91-0402B: Patient No. 04020, 04040, 03010, 03013, 03014; OC91-0907A: Patient No. 002, 006; OC91-0907B: Patient No. 07002, 15002, 009, 011, 018, 019, 021, 022, 07001, 003, 004, 007, 004BKC; OC92-1102: Patient No. 05014, 05004, 02030, 05005, 01002, 01001, 03019, 03007, 03011, 03016; OC92-1201: Patient No. 024, 5, X37, 33, 3, 9, 74, 73, 13, 11, 10

[26] Term: diarrhea. Study No. OC91-0402A: Patient No. 15008, 08008, 08016, 12003A; OC91-0402B: Patient No. 07016, 03010, 03040, 12007B; OC91-0907A: Patient No. 002, 2; OC91-0907B: Patient No. 021, 004

[27] Term: dry mouth. Study No. OC91-0402B: Patient No. 03009, 04011, 03010, 03040, 08020; OC91-0907A: Patient No. 002, 004; OC91-0907B: Patient No. 07003, 003, 004, 007; OC92-1102: Patient No. 05014, 03014, 03022; OC92-1201: Patient No. 3, 13

[28] Term: dyspepsia. Study No. OC91-0402A: Patient No. 07003; OC91-0402B: Patient No. 04001, 04040, 03040; 15005, 009; OC92-1102: Patient No. 01003, 05014, 03019; OC92-1201: Patient No. 023, 017, 1, 11

[29] Term: nausea. Study No. OC91-0402A: Patient No. 07003, 13003, 10002, 15008, 11006, 17027, 11007, 08003, 08010, 06005, 12001; OC91-0402B: Patient No. 04010, 04011, 04020, 03010, 03014, 12007B; OC91-0907A: Patient No. 002, 2, 007; OC91-0907B: Patient No. 07002, 3, 009, 011, 019, 021, 022, 07001, 001PGP, 001DR, 004; OC92-1102: Patient No. 02010, 05015, 05029, 05005, 03014, 03019, 03018, 03011, 06009, 06012; OC92-1201: Patient No. 024, 023, 017, 36, 35, 33, 1, 9, 74, 73, 13, 12, 11, 10

[30] Term: vomiting. Study No. OC91-0402A: Patient No. 11006, 06005; OC91-0402B: Patient No. 03010, 03039, 12003; OC91-0907A: Patient No. 2; OC91-0907B: Patient No. 07002, 15005, 3, 011, 018, 019, 022, 07001, 004; OC92-1102: Patient No. 02030, 05029, 03018; OC92-1201: Patient No. 017, 36, 35, 74, 12

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[33] Term: eructation. Study No. OC91-0402A: Patient No. 12001; OC91-0402B: Patient No. 03014

[34] Term: flatulence. Study No. OC91-0402A: Patient No. 11007; OC91-0402B: Patient No. 03013, 03014

[35] Term: gastrointestinal disorders. Study No. OC92-1102: Patient No. 02010, 01001, 03019

[36] Term: ileus. Labeling submission 3/25/97

[37] Term: asthenia. Study No. OC91-0402A: Patient No. 08003, 12001; OC91-0402B: Patient No. 04010, 04020, 12007B; OC91-0907B: Patient No. 15005, 3, 009, 018, 021, 001DR; OC92-1102: Patient No. 05029

[38] Term: chills. Study No. OC91-0402A: Patient No. 07003; OC91-0402B: Patient No.07016; OC91-0907A: Patient No. 2; OC91-0907B: Patient No. 003; OC92-1102: Patient No. 03018; OC92-1201: Patient No. 33

[39] Internal White Paper on Tolerance, 12-Mar-2003

[40] Term: withdrawal syndrome. Study No. OC91-0907B: Patient No. 018

[41] Term: edema. Study No. OC91-0907A: Patient No. 001MLB, 004; OC92-1102: Patient No. 05014

[42] Term: peripheral edema. Study No. OC91-0907BA: Patient No. 07001, 004BKC; OC92-1102: Patient No. 03016

[43] Term: malaise. Study No. OC91-0402B: Patient No. 12003; OC91-0907A: Patient No. 007

[44] Term: thirst. Study No. OC91-0402A: Patient No. 11006; OC91-0907A: Patient No. 004; OC92-1201: Patient No. 33

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[51] Term: anorexia. Study No. OC91-0402B: Patient No. 03013, 03014; OC91-0907B: Patient No. 07002, 15005, 019, 07001, 07003, 003, 004; OC92-1102: Patient No. 05005, 03011

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[53] Term: dehydration. Study No. OC91-0402A: Patient No. 15008; OC91-0907B: Patient No. 001DR

[54] Term: dizziness. Study No. OC91-0402A: Patient No. 02001, 07003, 11006, 17027, 11007, 02001, 08002, 08010, 06005; OC91-0402B: Patient No. 03009, 04001, 04010, 03010, 08020; OC91-0907A: Patient No. 002; OC91-0907B: Patient No. 15005, 018, 019, 021, 022, 07003, 001PGP, 004; OC92-1102: Patient No. 02010, 03014, 03025, 03019, 03011, 03016, 06012; OC92-1201: Patient No. 023, 017, 33, 9, 74, 73, 16

[55] Term: headache. Study No. OC91-0402A: Patient No. 13003, 10002, 11006, 08003, 08019, 08022, 12003A, 06027; OC91-0402B: Patient No. 04010, 18001, 03040, 12007B; OC91-0907A: Patient No. 002, 2, 006; OC91-0907B: Patient No. 07002, 018, 019, 022, 001PGP; OC92-1102: Patient No. 03005, 02010, 01003, 05015, 02027, 01002, 01001, 03025, 03019, 03018, 03007, 03016; OC92-1201: Patient No. 024, 023, 017, 5, X37, 35, 3, 1, 16, 13, 12, 10, 030

[56] Term: somnolence. Study No. OC91-0402A: Patient No. 07003, 13003, 10002, 15008, 08002, 08007, 08019, 08025; OC91-0402B: Patient No. 03007, 03009, 04020, 04027, 03010, 03014, 03039, 03040, 08012; OC91-0907A: Patient No. 002, 007; OC91-0907B: Patient No. 07002, 15002, 15005, 011, 018, 019, 021, 022, 07001, 07003, 004, 007; OC92-1102: Patient No. 01003, 02027, 03016; OC92-1201: Patient No. 5, X37, 36, 33, 1, 9, 74, 16, 13, 10, 030

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[63] Term: hypesthesia. Study No. OC91-0402A: Patient No. 02001; OC92-1201: Patient No. 74; OC91-0907A: 001MLB

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[65] Internal White Paper on Parasthesia, 20-Jun-2003

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[69] Term: syncope. Study No. OC91-0402B: Patient No. 12007B

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[73] Term: anxiety. Study No. OC91-0402B: Patient No. 03039, 12007B; OC91-0907A: Patient No. 002, 007; OC91-0907B: Patient No. 07002, 021, 07003; OC92-1102: Patient No. 03019; OC92-1201: Patient No. 36

[74] Term: confusion. Study No. OC91-0402A: Patient No. 15008; OC91-0402B: Patient No. 03009; OC91-0907B: Patient No. 15005, 021, 07001; OC92-1102: Patient No. 05029, 06009

[75] Term: insomnia. Study No. OC91-0402A: Patient No. 08016, 12001; OC91-0402B: Patient No. 08012, 08020; OC91-0907B: Patient No. 15002; OC92-1102: Patient No. 05005, 01001, 03022; OC92-1201: Patient No. 35, 3, 1, 9, 11

[76] Term: nervousness. Study No. OC91-0402A: Patient No. 11007, 08003; OC91-0402B: Patient No. 13001; OC91-0907A: Patient No. 007; OC91-0907B: Patient No. 009, 001DR; OC92-1102: Patient No. 01003, 03001; OC92-1201: Patient No. 16, 11

[77] Term: thought abnormalities. Study No. OC91-0402A: Patient No. 08011; OC91-0402B: Patient No. 08014; OC91-0907B: Patient No. 07002, 021, 022; OC92-1201: Patient No. 13

[78] Internal White Paper on Emotional Lability, 20-Jun-2003

[79] Term: emotional lability. Study No. OC91-0402BA: Patient No. 12003

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[85] Term: hallucinations. Study No. OC91-0907B: Patient No. 007

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[91] Term: dyspnea. Study No. OC91-0402A: Patient No. 08011; OC91-0907B: Patient No. 15005, 022, 07001, 007; OC92-1102: Patient No. 03019, 06009; OC92-1201: Patient No. 024

[92] Term: sweating. Study No. OC91-0402A: Patient No. 07003, 15008, 08010, 08011, 08018, 06005; OC91-0402B: Patient No. 07016, 07014, 03007, 03009, 04010, 04040, 07014; OC91-0907A: Patient No. 001EW; OC91-0907B: Patient No. 15005, 3, 009, 011, 019, 003; OC92-1102: Patient No. 03014; OC92-1201: Patient No. 35, 3, 74, 73

[93] Term: pruritus. Study No. OC91-0402A: Patient No. 11006, 08007, 08022, 06005; OC91-0402B: Patient No. 03007, 04027; OC91-0907A: Patient No. 001MLB, 007; OC91-0907B: Patient No. 014, 018, 022; OC92-1102: Patient No. 02027, 03025, 03019, 03007, 03011, 03016; OC92-1201: Patient No. 023, 36, 3, 1, 9, 74, 73, 16, 13, 11, 10

[94] Term: rash. Study No. OC91-0402A: Patient No. 08022; OC91-0907A: Patient No. 001MLB; OC91-0907B: Patient No. 014; OC92-1201: Patient No. 3

[95] Internal White Paper on Dry Skin, 20-Jun-2003

[96] Term: dry skin. Study No. OC91-0402A: Patient No. 08022

[97] Term: urticaria. Labeling Supplement, 25-Mar-1997

[98] Internal White Paper on Urticaria, 12-Mar-2003

[99] Term: urticaria. Study No. OC91-907B: Patient No. 014

[100] Internal White Paper on Hypotension, 12-Mar-2003

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[118] Chromosomal Aberration Test in Human Lymphocytes with Oxycodone HCl solution and Oxycodone injectable form containing dimer impurity: 778436.

[119] Oxycodone Ames Bacterial Mutation Test: DSE-149-GLP.

[120] L5175 TK +/- Mouse Lymphoma Forward Mutation Assay with Oxycodone HCl: DSE-150-GLP.

[121] Chromosomal aberration test in human lymphocytes with Oxycodone HCl: DSE-151-GLP.

[122] Oxycodone In vivo (Oral Dosing) Mouse Micronucleus Assay with Oxycodone HCl: DSE-152-GLP.